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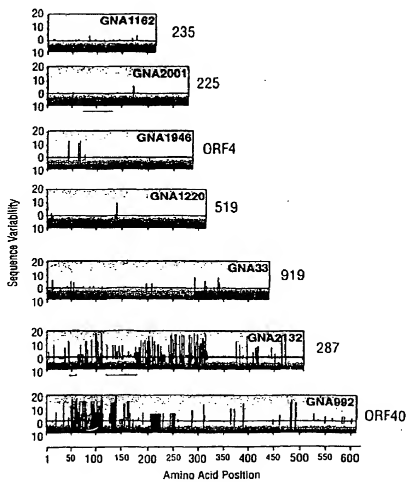
(57) Abstract

To ensure maximum cross-strain recognition and reactivity, regions of proteins that are conserved between different Neisserial species, serogroups and strains can be used. The invention provides proteins which comprise stretches of amino acid sequence that are shared across the majority of *Neisseria*, particularly *N. meningitidis* and *N.gonorrhoeae*.



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CONSERVED NEISSERIAL ANTIGENS

The contents of all documents cited herein are incorporated by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to conserved antigens from the *Neisseria* bacteria.

BACKGROUND ART

Neisseria meningitidis and *Neisseria gonorrhoeae* are non-motile, gram negative diplococci that are pathogenic in humans.

Based on the organism's capsular polysaccharide, 12 serogroups of *N.meningitidis* have been identified. Group A is the pathogen most often implicated in epidemic disease in sub-Saharan Africa. Serogroups B and C are responsible for the vast majority of cases in the United States and in most developed countries. Serogroups W135 and Y are responsible for the rest of the cases in the United States and developed countries.

The meningococcal vaccine currently in use is a tetravalent polysaccharide vaccine composed of serogroups A, C, Y and W135. This approach cannot be used for Meningococcus B, however, because the menB capsular polysaccharide is a polymer of α(2-8)-linked *N*-acetyl neuraminic acid that is also present in mammalian tissue. One approach to a menB vaccine uses mixtures of outer membrane proteins (OMPs) To overcome the antigenic variability, multivalent vaccines containing up to nine different porins have been constructed [*eg.* Poolman (1992) Development of a meningococcal vaccine. *Infect. Agents Dis.* 4:13-28]. Additional proteins to be used in outer membrane vaccines have been the opa and opc proteins, but none of these approaches have been able to overcome the antigenic variability [*eg.* Ala'Aldeen & Borriello (1996) The meningococcal transferrin-binding proteins 1 and 2 are both surface exposed and generate bactericidal antibodies capable of killing homologous and heterologous strains. *Vaccine* 14(1):49-53].

A large number of Neisserial protein and nucleotide sequences are disclosed in WO99/24578, WO99/36544, WO99/57280 and WO00/22430. The contents of these four applications are incorporated herein by reference. Comprehensive sequence data from strain MC58 is disclosed in Tettelin *et al.* [*Science* (2000) 287:1809-1815], the contents of which are also incorporated herein by reference.

DESCRIPTION OF THE INVENTION

To ensure maximum cross-strain recognition and reactivity, regions of proteins that are conserved between different Neisserial species, serogroups and strains can be used. The invention therefore provides proteins which comprise stretches of amino acid sequence that are shared across the majority of *Neisseria*, particularly *N.meningitidis* and *N.gonorrhoeae*.

The invention provides a protein comprising a fragment of a Neisserial protein, wherein said fragment consists of *n* consecutive conserved amino acids, with the proviso that the invention does not include within its scope full-length Neisserial proteins. Depending on the particular protein, *n* is 7 or more (*eg.* 8, 10, 12, 14, 16, 18, 20 or more). The fragment preferably comprises an antigenic or immunogenic region of the Neisserial protein.

A "conserved" amino acid is one that is present in a particular Neisserial protein in at least *x*% of *Neisseria*. The value of *x* may be 50% or more *eg.* 66%, 75%, 80%, 90%, 95% or even 100% (*ie.* the amino acid is found in the protein in question in all *Neisseria*).

In order to determine whether an amino acid is "conserved" in a particular Neisserial protein, it is necessary to compare that amino acid residue in the sequences of the protein in question from a plurality of different *Neisseria* (a "reference population"). The reference population may include a number of different *Neisseria* species (preferably *N.meningitidis* and *N.gonorrhoeae*) or may include a single species. The reference population may include a number of different serogroups of a particular species (such as the A, B, C, W135, X, Y, Z and 29E serogroups of *N.meningitidis*) or a single serogroup. The reference population may also include a number of different strains from a particular serogroup (such as the NG6/88, BZ198, NG3/88, 297-0, BZ147, BZ169, 528, BZ133, NGE31, NGH38, NGH15, BZ232, BZ83, and 44/76 strains of *N.meningitidis* B). A preferred reference population consists of the 5 most common strains of *N. meningitidis* and/or the 5 most common strains of *N.gonorrhoeae*.

The reference population preferably comprises *k* strains taken from *k* different branches of a suitable phylogenetic tree, such as those disclosed in (a) Ni *et al.* (1992) *Epidemiol Infect* 109:227-239 (b) Wolff *et al.* (1992) *Nucleic Acids Res* 20:4657 (c) Bygraves & Maiden (1992) *J. Gen. Microbiol.* 138:523-531 (d) Caugant *et al.* (1987) *J. Bacteriol.* 69:2781-2792. Another phylogenetic tree that can be used is shown in Figure 8 herein, and another in Figure 9b.

It will be appreciated that a particular species, serogroup or strain should only be included in the reference population if it encodes the protein in which the amino acid in question is located. In

the case of amino acids within ORF40 described below, for instance, the reference population should not include *N.gonorrhoeae* because this species does not contain ORF40.

For proteins found in both *N.meningitidis* and *N.gonorrhoeae*, therefore, a preferred reference population comprises:

- *N.meningitidis* A, strain Z2491
- *N.meningitidis* B, strains NG6/88
- *N.meningitidis* W, strains A22
- *N.gonorrhoeae*, strain Ng F62

These are described in (a) Seiler A. *et al.* (1996) *Mol. Microbiol.* 19(4):841-856 (b) Maiden *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95:3140-3145 (c) Virji *et al.* (1992) *Mol. Microbiol.* 6:1271-1279 (d) Dempsey *et al.* (1991) *J. Bacteriol.* 173:5476-5486.

For proteins found only in *N.meningitidis*, however, a preferred reference population comprises:

- *N.meningitidis* A, strain Z2491
- *N.meningitidis* B, strains NG6/88
- *N.meningitidis* W, strains A22

Amino acid sequences of different *Neissieriae* can easily be compared using computers. This will typically involve the alignment of a number of sequences using an algorithm such as CLUSTAL [Thompson *et al.* (1994) *Nucleic Acids Res* 22:4673-4680; *Trends Biochem Sci* (1998) 23:403-405] or, preferably, PILEUP [part of the GCG Wisconsin package, preferably version 9.0].

Conserved amino acids are readily apparent in a multiple sequence alignment – at the amino acid position in question a majority of the aligned sequences will contain a particular amino acid. Conserved amino acids can be made more visually apparent by using a program such as BOXSHADE [available, for instance, at the NIH on-line], PRETTYBOX [GCG Wisconsin, version 10] or JALVIEW [available on-line at EBI].

The protein preferably comprises a fragment of one of the proteins disclosed in WO99/24578, WO99/36544, WO99/57280 or WO00/22430, or of one of the 2158 ORFs disclosed in Tettelin *et al.* [*Science* (2000) 287:1809-1815]. More particularly, it preferably comprises a fragment of one or more of ORF4, ORF40, ORF46, protein 225, protein 235, protein 287, protein 519, protein 726, protein 919 and protein 953 disclosed therein (see examples herein). Typically, the

protein of the invention will not comprise a protein sequence explicitly disclosed in WO99/24578, WO99/36544, WO99/57280, WO00/22430, or Tettelin *et al.*

The invention also provides a protein comprising one of the sequences shown in the Figures.

The proteins of the invention can, of course, be prepared by various means (*eg.* recombinant expression, native expression, purification from cell culture, chemical synthesis *etc.*) and in various forms (*eg.* native, fusions *etc.*). They are preferably prepared in substantially pure form (*ie.* substantially free from other Neisserial or host cell proteins)

According to a further aspect, the invention provides antibodies which bind to these proteins. These may be polyclonal or monoclonal and may be produced by any suitable means.

According to a further aspect, the invention provides nucleic acid encoding the proteins of the invention. It should also be appreciated that the invention provides nucleic acid comprising sequences complementary to these (*eg.* for antisense or probing purposes).

Furthermore, the invention provides nucleic acid which can hybridise to the *N.meningitidis* nucleic acid disclosed in the examples, preferably under "high stringency" conditions (*eg.* 65°C in a 0.1xSSC, 0.5% SDS solution).

Nucleic acid according to the invention can, of course, be prepared in many ways (*eg.* by chemical synthesis, from genomic or cDNA libraries, from the organism itself *etc.*) and can take various forms (*eg.* single stranded, double stranded, vectors, probes *etc.*).

In addition, the term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones, and also peptide nucleic acids (PNA) *etc.*

According to a further aspect, the invention provides vectors comprising nucleotide sequences of the invention (*eg.* expression vectors) and host cells transformed with them.

According to a further aspect, the invention provides compositions comprising protein, antibody, and/or nucleic acid according to the invention. These compositions may be suitable as vaccines, for instance, or as diagnostic reagents, or as immunogenic compositions.

The invention also provides nucleic acid, protein, or antibody according to the invention for use as medicaments (*eg.* as vaccines) or as diagnostic reagents. It also provides the use of nucleic acid, protein, or antibody according to the invention in the manufacture of: (i) a medicament for treating or preventing infection due to Neisserial bacteria; (ii) a diagnostic reagent for detecting

the presence of Neisserial bacteria or of antibodies raised against Neisserial bacteria; and/or (iii) a reagent which can raise antibodies against Neisserial bacteria. The use is preferably applicable to all species of *Neisseria*.

Where a Neisserial protein contains more than *q%* conserved amino acids, the invention provides the use of the Neisserial protein, or a fragment thereof, as a non-strain-specific protein that exhibits cross-reactivity between many species, serogroups and strains. The value of *q* may be 50%, 60%, 75%, 80%, 90%, 95% or even 100%.

The invention also provides a method of treating a patient, comprising administering to the patient a therapeutically effective amount of nucleic acid, protein, and/or antibody according to the invention.

According to further aspects, the invention provides various processes.

A process for producing proteins of the invention is provided, comprising the step of culturing a host cell according to the invention under conditions which induce protein expression.

A process for producing protein or nucleic acid of the invention is provided, wherein the protein or nucleic acid is synthesised in part or in whole using chemical means.

A process for detecting polynucleotides of the invention is provided, comprising the steps of: (a) contacting a nucleic probe according to the invention with a biological sample under hybridizing conditions to form duplexes; and (b) detecting said duplexes.

A process for detecting proteins of the invention is provided, comprising the steps of: (a) contacting an antibody according to the invention with a biological sample under conditions suitable for the formation of an antibody-antigen complexes; and (b) detecting said complexes.

A summary of standard techniques and procedures which may be employed in order to perform the invention (*eg.* to utilise the disclosed sequences for vaccination or diagnostic purposes) follows. This summary is not a limitation on the invention but, rather, gives examples that may be used, but are not required.

<u>*General*</u>

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature *eg.* Sambrook *Molecular Cloning; A Laboratory Manual, Second Edition* (1989); *DNA Cloning, Volumes I and ii* (D.N Glover ed. 1985); *Oligonucleotide*

Synthesis (M.J. Gait ed, 1984); *Nucleic Acid Hybridization* (B.D. Hames & S.J. Higgins eds. 1984); *Transcription and Translation* (B.D. Hames & S.J. Higgins eds. 1984); *Animal Cell Culture* (R.I. Freshney ed. 1986); *Immobilized Cells and Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide to Molecular Cloning* (1984); the *Methods in Enzymology* series (Academic Press, Inc.), especially volumes 154 & 155; *Gene Transfer Vectors for Mammalian Cells* (J.H. Miller and M.P. Calos eds. 1987, Cold Spring Harbor Laboratory); Mayer and Walker, eds. (1987), *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Scopes, (1987) *Protein Purification: Principles and Practice*, Second Edition (Springer-Verlag, N.Y.), and *Handbook of Experimental Immunology, Volumes I-IV* (D.M. Weir and C. C. Blackwell eds 1986).

Standard abbreviations for nucleotides and amino acids are used in this specification.

All publications, patents, and patent applications cited herein are incorporated in full by reference. In particular, the contents of international patent applications WO99/24578, WO99/36544, WO99/57280 and WO00/22430 are incorporated herein.

Definitions

A composition containing X is "substantially free of" Y when at least 85% by weight of the total X+Y in the composition is X. Preferably, X comprises at least about 90% by weight of the total of X+Y in the composition, more preferably at least about 95% or even 99% by weight.

The term "comprising" means "including" as well as "consisting" *eg.* a composition "comprising" X may consist exclusively of X or may include something additional to X, such as X+Y.

The term "heterologous" refers to two biological components that are not found together in nature. The components may be host cells, genes, or regulatory regions, such as promoters. Although the heterologous components are not found together in nature, they can function together, as when a promoter heterologous to a gene is operably linked to the gene. Another example is where a Neisserial sequence is heterologous to a mouse host cell. A further examples would be two epitopes from the same or different proteins which have been assembled in a single protein in an arrangement not found in nature.

An "origin of replication" is a polynucleotide sequence that initiates and regulates replication of polynucleotides, such as an expression vector. The origin of replication behaves as an autonomous unit of polynucleotide replication within a cell, capable of replication under its own control. An origin of replication may be needed for a vector to replicate in a particular host cell. With certain origins of replication, an expression vector can be reproduced at a high copy number in the presence of the appropriate

proteins within the cell. Examples of origins are the autonomously replicating sequences, which are effective in yeast; and the viral T-antigen, effective in COS-7 cells.

A "mutant" sequence is defined as DNA, RNA or amino acid sequence differing from but having sequence identity with the native or disclosed sequence. Depending on the particular sequence, the degree of sequence identity between the native or disclosed sequence and the mutant sequence is preferably greater than 50% (*eg.* 60%, 70%, 80%, 90%, 95%, 99% or more, calculated using the Smith-Waterman algorithm as described above). As used herein, an "allelic variant" of a nucleic acid molecule, or region, for which nucleic acid sequence is provided herein is a nucleic acid molecule, or region, that occurs essentially at the same locus in the genome of another or second isolate, and that, due to natural variation caused by, for example, mutation or recombination, has a similar but not identical nucleic acid sequence. A coding region allelic variant typically encodes a protein having similar activity to that of the protein encoded by the gene to which it is being compared. An allelic variant can also comprise an alteration in the 5' or 3' untranslated regions of the gene, such as in regulatory control regions (*eg.* see US patent 5,753,235).

Expression systems

The Neisserial nucleotide sequences can be expressed in a variety of different expression systems; for example those used with mammalian cells, baculoviruses, plants, bacteria, and yeast.

i. Mammalian Systems

Mammalian expression systems are known in the art. A mammalian promoter is any DNA sequence capable of binding mammalian RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiating region, which is usually placed proximal to the 5' end of the coding sequence, and a TATA box, usually located 25-30 base pairs (bp) upstream of the transcription initiation site. The TATA box is thought to direct RNA polymerase II to begin RNA synthesis at the correct site. A mammalian promoter will also contain an upstream promoter element, usually located within 100 to 200 bp upstream of the TATA box. An upstream promoter element determines the rate at which transcription is initiated and can act in either orientation [Sambrook et al. (1989) "Expression of Cloned Genes in Mammalian Cells." In *Molecular Cloning: A Laboratory Manual, 2nd ed.*].

Mammalian viral genes are often highly expressed and have a broad host range; therefore sequences encoding mammalian viral genes provide particularly useful promoter sequences. Examples include the SV40 early promoter, mouse mammary tumor virus LTR promoter, adenovirus major late promoter (Ad MLP), and herpes simplex virus promoter. In addition, sequences derived from non-viral genes, such as the murine metallotheionein gene, also provide useful promoter sequences. Expression may be either

constitutive or regulated (inducible), depending on the promoter can be induced with glucocorticoid in hormone-responsive cells.

The presence of an enhancer element (enhancer), combined with the promoter elements described above, will usually increase expression levels. An enhancer is a regulatory DNA sequence that can stimulate transcription up to 1000-fold when linked to homologous or heterologous promoters, with synthesis beginning at the normal RNA start site. Enhancers are also active when they are placed upstream or downstream from the transcription initiation site, in either normal or flipped orientation, or at a distance of more than 1000 nucleotides from the promoter [Maniatis et al. (1987) *Science 236:*1237; Alberts et al. (1989) *Molecular Biology of the Cell*, 2nd ed.]. Enhancer elements derived from viruses may be particularly useful, because they usually have a broader host range. Examples include the SV40 early gene enhancer [Dijkema et al (1985) *EMBO J. 4*:761] and the enhancer/promoters derived from the long terminal repeat (LTR) of the Rous Sarcoma Virus [Gorman et al. (1982b) *Proc. Natl. Acad. Sci. 79*:6777] and from human cytomegalovirus [Boshart et al. (1985) *Cell 41*:521]. Additionally, some enhancers are regulatable and become active only in the presence of an inducer, such as a hormone or metal ion [Sassone-Corsi and Borelli (1986) *Trends Genet. 2*:215; Maniatis et al. (1987) *Science* 236:1237].

A DNA molecule may be expressed intracellularly in mammalian cells. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the ATG start codon. If desired, the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provides for secretion of the foreign protein in mammalian cells. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell. The adenovirus triparite leader is an example of a leader sequence that provides for secretion of a foreign protein in mammalian cells.

Usually, transcription termination and polyadenylation sequences recognized by mammalian cells are regulatory regions located 3' to the translation stop codon and thus, together with the promoter elements, flank the coding sequence. The 3' terminus of the mature mRNA is formed by site-specific post-transcriptional cleavage and polyadenylation [Birnstiel et al. (1985) *Cell 41*:349; Proudfoot and Whitelaw (1988) "Termination and 3' end processing of eukaryotic RNA. In *Transcription and splicing* (ed. B.D. Hames and D.M. Glover); Proudfoot (1989) *Trends Biochem. Sci. 14*:105]. These sequences direct the

transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Examples of transcription terminater/polyadenylation signals include those derived from SV40 [Sambrook et al (1989) "Expression of cloned genes in cultured mammalian cells." In *Molecular Cloning: A Laboratory Manual*].

Usually, the above described components, comprising a promoter, polyadenylation signal, and transcription termination sequence are put together into expression constructs. Enhancers, introns with functional splice donor and acceptor sites, and leader sequences may also be included in an expression construct, if desired. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as mammalian cells or bacteria. Mammalian replication systems include those derived from animal viruses, which require trans-acting factors to replicate. For example, plasmids containing the replication systems of papovaviruses, such as SV40 [Gluzman (1981) *Cell 23*:175] or polyomavirus, replicate to extremely high copy number in the presence of the appropriate viral T antigen. Additional examples of mammalian replicons include those derived from bovine papillomavirus and Epstein-Barr virus. Additionally, the replicon may have two replicaton systems, thus allowing it to be maintained, for example, in mammalian cells for expression and in a prokaryotic host for cloning and amplification. Examples of such mammalian-bacteria shuttle vectors include pMT2 [Kaufman et al. (1989) *Mol. Cell. Biol. 9*:946] and pHEBO [Shimizu et al. (1986) *Mol. Cell. Biol. 6*:1074].

The transformation procedure used depends upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*eg.* Hep G2), and a number of other cell lines.

ii. Baculovirus Systems

The polynucleotide encoding the protein can also be inserted into a suitable insect expression vector, and is operably linked to the control elements within that vector. Vector construction employs techniques which are known in the art. Generally, the components of the expression system include a transfer vector, usually a bacterial plasmid, which contains both a fragment of the baculovirus genome, and a convenient restriction site for insertion of the heterologous gene or genes to be expressed; a wild type baculovirus with a sequence homologous to the baculovirus-specific fragment in the transfer vector (this allows for the homologous

recombination of the heterologous gene in to the baculovirus genome); and appropriate insect host cells and growth media.

After inserting the DNA sequence encoding the protein into the transfer vector, the vector and the wild type viral genome are transfected into an insect host cell where the vector and viral genome are allowed to recombine. The packaged recombinant virus is expressed and recombinant plaques are identified and purified. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *inter alia*, Invitrogen, San Diego CA ("MaxBac" kit). These techniques are generally known to those skilled in the art and fully described in Summers and Smith, *Texas Agricultural Experiment Station Bulletin No. 1555* (1987) (hereinafter "Summers and Smith").

Prior to inserting the DNA sequence encoding the protein into the baculovirus genome, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are usually assembled into an intermediate transplacement construct (transfer vector). This construct may contain a single gene and operably linked regulatory elements; multiple genes, each with its owned set of operably linked regulatory elements; or multiple genes, regulated by the same set of regulatory elements. Intermediate transplacement constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as a bacterium. The replicon will have a replication system, thus allowing it to be maintained in a suitable host for cloning and amplification.

Currently, the most commonly used transfer vector for introducing foreign genes into AcNPV is pAc373. Many other vectors, known to those of skill in the art, have also been designed. These include, for example, pVL985 (which alters the polyhedrin start codon from ATG to ATT, and which introduces a BamHI cloning site 32 basepairs downstream from the ATT; see Luckow and Summers, *Virology* (1989) *17*:31.

The plasmid usually also contains the polyhedrin polyadenylation signal (Miller et al. (1988) *Ann. Rev. Microbiol.*, *42*:177) and a prokaryotic ampicillin-resistance (*amp*) gene and origin of replication for selection and propagation in *E. coli*.

Baculovirus transfer vectors usually contain a baculovirus promoter. A baculovirus promoter is any DNA sequence capable of binding a baculovirus RNA polymerase and initiating the downstream (5' to 3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A

baculovirus transfer vector may also have a second domain called an enhancer, which, if present, is usually distal to the structural gene. Expression may be either regulated or constitutive.

Structural genes, abundantly transcribed at late times in a viral infection cycle, provide particularly useful promoter sequences. Examples include sequences derived from the gene encoding the viral polyhedron protein, Friesen et al., (1986) "The Regulation of Baculovirus Gene Expression," in: *The Molecular Biology of Baculoviruses* (ed. Walter Doerfler); EPO Publ. Nos. 127 839 and 155 476; and the gene encoding the p10 protein, Vlak et al., (1988), *J. Gen. Virol. 69*:765.

DNA encoding suitable signal sequences can be derived from genes for secreted insect or baculovirus proteins, such as the baculovirus polyhedrin gene (Carbonell et al. (1988) *Gene*, *73*:409). Alternatively, since the signals for mammalian cell posttranslational modifications (such as signal peptide cleavage, proteolytic cleavage, and phosphorylation) appear to be recognized by insect cells, and the signals required for secretion and nuclear accumulation also appear to be conserved between the invertebrate cells and vertebrate cells, leaders of non-insect origin, such as those derived from genes encoding human α-interferon, Maeda et al., (1985), *Nature 315*:592; human gastrin-releasing peptide, Lebacq-Verheyden et al., (1988), *Molec. Cell. Biol. 8*:3129; human IL-2, Smith et al., (1985) *Proc. Nat'l Acad. Sci. USA*, *82*:8404; mouse IL-3, (Miyajima et al., (1987) *Gene 58*:273; and human glucocerebrosidase, Martin et al. (1988) *DNA*, *7*:99, can also be used to provide for secretion in insects.

A recombinant polypeptide or polyprotein may be expressed intracellularly or, if it is expressed with the proper regulatory sequences, it can be secreted. Good intracellular expression of nonfused foreign proteins usually requires heterologous genes that ideally have a short leader sequence containing suitable translation initiation signals preceding an ATG start signal. If desired, methionine at the N-terminus may be cleaved from the mature protein by *in vitro* incubation with cyanogen bromide.

Alternatively, recombinant polyproteins or proteins which are not naturally secreted can be secreted from the insect cell by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provides for secretion of the foreign protein in insects. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the translocation of the protein into the endoplasmic reticulum.

After insertion of the DNA sequence and/or the gene encoding the expression product precursor of the protein, an insect cell host is co-transformed with the heterologous DNA of the transfer vector and the genomic DNA of wild type baculovirus -- usually by co-transfection. The promoter and transcription termination sequence of the construct will usually comprise a 2-5kb section of the baculovirus genome.

Methods for introducing heterologous DNA into the desired site in the baculovirus virus are known in the art. (See Summers and Smith *supra*; Ju et al. (1987); Smith et al., *Mol. Cell. Biol.* (1983) *3*:2156; and Luckow and Summers (1989)). For example, the insertion can be into a gene such as the polyhedrin gene, by homologous double crossover recombination; insertion can also be into a restriction enzyme site engineered into the desired baculovirus gene. Miller et al., (1989), *Bioessays 4*:91.The DNA sequence, when cloned in place of the polyhedrin gene in the expression vector, is flanked both 5' and 3' by polyhedrin-specific sequences and is positioned downstream of the polyhedrin promoter.

The newly formed baculovirus expression vector is subsequently packaged into an infectious recombinant baculovirus. Homologous recombination occurs at low frequency (between about 1% and about 5%); thus, the majority of the virus produced after cotransfection is still wild-type virus. Therefore, a method is necessary to identify recombinant viruses. An advantage of the expression system is a visual scre(allowing recombinant viruses to be distinguished. The polyhedrin protein, which is produced by the native virus, is produced at very high levels in the nuclei of infected cells at late times after viral infection. Accumulated polyhedrin protein forms occlusion bodies that also contain embedded particles. These occlusion bodies, up to 15 μm in size, are highly refractile, giving them a bright shiny appearance that is readily visualized under the light microscope. Cells infected with recombinant viruses lack occlusion bodies. To distinguish recombinant virus from wild-type virus, the transfection supernatant is plaqued onto a monolayer of insect cells by techniques known to those skilled in the art. Namely, the plaques are screened under the light microscope for the presence (indicative of wild-type virus) or absence (indicative of recombinant virus) of occlusion bodies. "Current Protocols in Microbiology" Vol. 2 (Ausubel et al. eds) at 16.8 (Supp. 10, 1990); Summers and Smith, *supra*; Miller et al. (1989).

Recombinant baculovirus expression vectors have been developed for infection into several insect cells. For example, recombinant baculoviruses have been developed for, *inter alia*: *Aedes aegypti* , *Autographa californica*, *Bombyx mori*, *Drosophila melanogaster*, *Spodoptera frugiperda*, and *Trichoplusia ni* (WO 89/046699; Carbonell et al., (1985) *J. Virol. 56*:153; Wright (1986) *Nature 321*:718; Smith et al., (1983) *Mol. Cell. Biol. 3*:2156; and see generally, Fraser, *et al.* (1989) *In Vitro Cell. Dev. Biol. 25*:225).

Cells and cell culture media are commercially available for both direct and fusion expression of heterologous polypeptides in a baculovirus/expression system; cell culture technology is generally known to those skilled in the art. *See, eg.* Summers and Smith *supra.*

The modified insect cells may then be grown in an appropriate nutrient medium, which allows for stable maintenance of the plasmid(s) present in the modified insect host. Where the expression product gene is under inducible control, the host may be grown to high density, and expression induced. Alternatively,

where expression is constitutive, the product will be continuously expressed into the medium and the nutrient medium must be continuously circulated, while removing the product of interest and augmenting depleted nutrients. The product may be purified by such techniques as chromatography, eg. HPLC, affinity chromatography, ion exchange chromatography, etc.; electrophoresis; density gradient centrifugation; solvent extraction, or the like. As appropriate, the product may be further purified, as required, so as to remove substantially any insect proteins which are also secreted in the medium or result from lysis of insect cells, so as to provide a product which is at least substantially free of host debris, eg. proteins, lipids and polysaccharides.

In order to obtain protein expression, recombinant host cells derived from the transformants are incubated under conditions which allow expression of the recombinant protein encoding sequence. These conditions will vary, dependent upon the host cell selected. However, the conditions are readily ascertainable to those of ordinary skill in the art, based upon what is known in the art.

iii. Plant Systems

There are many plant cell culture and whole plant genetic expression systems known in the art. Exemplary plant cellular genetic expression systems include those described in patents, such as: US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, *Phytochemistry* 30:3861-3863 (1991). Descriptions of plant protein signal peptides may be found in addition to the references described above in Vaulcombe et al., *Mol. Gen. Genet.* 209:33-40 (1987); Chandler et al., *Plant Molecular Biology* 3:407-418 (1984); Rogers, *J. Biol. Chem.* 260:3731-3738 (1985); Rothstein et al., *Gene* 55:353-356 (1987); Whittier et al., Nucleic Acids Research 15:2515-2535 (1987); Wirsel et al., *Molecular Microbiology* 3:3-14 (1989); Yu et al., *Gene* 122:247-253 (1992). A description of the regulation of plant gene expression by the phytohormone, gibberellic acid and secreted enzymes induced by gibberellic acid can be found in R.L. Jones and J. MacMillin, Gibberellins: in: *Advanced Plant Physiology*,. Malcolm B. Wilkins, ed., 1984 Pitman Publishing Limited, London, pp. 21-52. References that describe other metabolically-regulated genes: Sheen, *Plant Cell*, 2:1027-1038(1990); Maas et al., *EMBO J.* 9:3447-3452 (1990); Benkel and Hickey, *Proc. Natl. Acad. Sci.* 84:1337-1339 (1987)

Typically, using techniques known in the art, a desired polynucleotide sequence is inserted into an expression cassette comprising genetic regulatory elements designed for operation in plants. The expression cassette is inserted into a desired expression vector with companion sequences upstream and downstream from the expression cassette suitable for expression in a plant host. The companion sequences will be of plasmid or viral origin and provide necessary characteristics to the vector to permit the vectors to move DNA from an original cloning host, such as bacteria, to the desired plant host. The basic bacterial/plant vector construct will preferably provide a broad host range prokaryote replication origin; a

prokaryote selectable marker; and, for Agrobacterium transformations, T DNA sequences for Agrobacterium-mediated transfer to plant chromosomes. Where the heterologous gene is not readily amenable to detection, the construct will preferably also have a selectable marker gene suitable for determining if a plant cell has been transformed. A general review of suitable markers, for example for the members of the grass family, is found in Wilmink and Dons, 1993, *Plant Mol. Biol. Reptr*, 11(2):165-185.

Sequences suitable for permitting integration of the heterologous sequence into the plant genome are also recommended. These might include transposon sequences and the like for homologous recombination as well as Ti sequences which permit random insertion of a heterologous expression cassette into a plant genome. Suitable prokaryote selectable markers include resistance toward antibiotics such as ampicillin or tetracycline. Other DNA sequences encoding additional functions may also be present in the vector, as is known in the art.

The nucleic acid molecules of the subject invention may be included into an expression cassette for expression of the protein(s) of interest. Usually, there will be only one expression cassette, although two or more are feasible. The recombinant expression cassette will contain in addition to the heterologous protein encoding sequence the following elements, a promoter region, plant 5' untranslated sequences, initiation codon depending upon whether or not the structural gene comes equipped with one, and a transcription and translation termination sequence. Unique restriction enzyme sites at the 5' and 3' ends of the cassette allow for easy insertion into a pre-existing vector.

A heterologous coding sequence may be for any protein relating to the present invention. The sequence encoding the protein of interest will encode a signal peptide which allows processing and translocation of the protein, as appropriate, and will usually lack any sequence which might result in the binding of the desired protein of the invention to a membrane. Since, for the most part, the transcriptional initiation region will be for a gene which is expressed and translocated during germination, by employing the signal peptide which provides for translocation, one may also provide for translocation of the protein of interest. In this way, the protein(s) of interest will be translocated from the cells in which they are expressed and may be efficiently harvested. Typically secretion in seeds are across the aleurone or scutellar epithelium layer into the endosperm of the seed. While it is not required that the protein be secreted from the cells in which the protein is produced, this facilitates the isolation and purification of the recombinant protein.

Since the ultimate expression of the desired gene product will be in a eucaryotic cell it is desirable to determine whether any portion of the cloned gene contains sequences which will be processed out as introns by the host's splicosome machinery. If so, site-directed mutagenesis of the "intron" region may be

conducted to prevent losing a portion of the genetic message as a false intron code, Reed and Maniatis, *Cell* 41:95-105, 1985.

The vector can be microinjected directly into plant cells by use of micropipettes to mechanically transfer the recombinant DNA. Crossway, *Mol. Gen. Genet*, 202:179-185, 1985. The genetic material may also be transferred into the plant cell by using polyethylene glycol, Krens, et al., *Nature*, 296, 72-74, 1982. Another method of introduction of nucleic acid segments is high velocity ballistic penetration by small particles with the nucleic acid either within the matrix of small beads or particles, or on the surface, Klein, et al., *Nature*, 327, 70-73, 1987 and Knudsen and Muller, 1991, *Planta*, 185:330-336 teaching particle bombardment of barley endosperm to create transgenic barley. Yet another method of introduction would be fusion of protoplasts with other entities, either minicells, cells, lysosomes or other fusible lipid-surfaced bodies, Fraley, et al., *Proc. Natl. Acad. Sci. USA*, 79, 1859-1863, 1982.

The vector may also be introduced into the plant cells by electroporation. (Fromm et al., *Proc. Natl Acad. Sci. USA* 82:5824, 1985). In this technique, plant protoplasts are electroporated in the presence of plasmids containing the gene construct. Electrical impulses of high field strength reversibly permeabilize biomembranes allowing the introduction of the plasmids. Electroporated plant protoplasts reform the cell wall, divide, and form plant callus.

All plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be transformed by the present invention so that whole plants are recovered which contain the transferred gene. It is known that practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of sugarcane, sugar beet, cotton, fruit and other trees, legumes and vegetables. Some suitable plants include, for example, species from the genera *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersion*, *Nicotiana*, *Solanum*, *Petunia*, *Digitalis*, *Majorana*, *Cichorium*, *Helianthus*, *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Hererocallis*, *Nemesia*, *Pelargonium*, *Panicum*, *Pennisetum*, *Ranunculus*, *Senecio*, *Salpiglossis*, *Cucumis*, *Browaalia*, *Glycine*, *Lolium*, *Zea*, *Triticum*, *Sorghum*, and *Datura*.

Means for regeneration vary from species to species of plants, but generally a suspension of transformed protoplasts containing copies of the heterologous gene is first provided. Callus tissue is formed and shoots may be induced from callus and subsequently rooted. Alternatively, embryo formation can be induced from the protoplast suspension. These embryos germinate as natural embryos to form plants. The culture media will generally contain various amino acids and hormones, such as auxin and cytokinins. It is also advantageous to add glutamic acid and proline to the medium, especially for such species as corn and

alfalfa. Shoots and roots normally develop simultaneously. Efficient regeneration will depend on the medium, on the genotype, and on the history of the culture. If these three variables are controlled, then regeneration is fully reproducible and repeatable.

In some plant cell culture systems, the desired protein of the invention may be excreted or alternatively, the protein may be extracted from the whole plant. Where the desired protein of the invention is secreted into the medium, it may be collected. Alternatively, the embryos and embryoless-half seeds or other plant tissue may be mechanically disrupted to release any secreted protein between cells and tissues. The mixture may be suspended in a buffer solution to retrieve soluble proteins. Conventional protein isolation and purification methods will be then used to purify the recombinant protein. Parameters of time, temperature pH, oxygen, and volumes will be adjusted through routine methods to optimize expression and recovery of heterologous protein.

<u>iv. Bacterial Systems</u>

Bacterial expression techniques are known in the art. A bacterial promoter is any DNA sequence capable of binding bacterial RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A bacterial promoter may also have a second domain called an operator, that may overlap an adjacent RNA polymerase binding site at which RNA synthesis begins. The operator permits negative regulated (inducible) transcription, as a gene repressor protein may bind the operator and thereby inhibit transcription of a specific gene. Constitutive expression may occur in the absence of negative regulatory elements, such as the operator. In addition, positive regulation may be achieved by a gene activator protein binding sequence, which, if present is usually proximal (5') to the RNA polymerase binding sequence. An example of a gene activator protein is the catabolite activator protein (CAP), which helps initiate transcription of the lac operon in Escherichia coli (E. coli) [Raibaud *et al.* (1984) *Annu. Rev. Genet. 18*:173]. Regulated expression may therefore be either positive or negative, thereby either enhancing or reducing transcription.

Sequences encoding metabolic pathway enzymes provide particularly useful promoter sequences. Examples include promoter sequences derived from sugar metabolizing enzymes, such as galactose, lactose (*lac*) [Chang *et al.* (1977) *Nature 198*:1056], and maltose. Additional examples include promoter sequences derived from biosynthetic enzymes such as tryptophan (*trp*) [Goeddel *et al.* (1980) *Nuc. Acids Res. 8*:4057; Yelverton *et al.* (1981) *Nucl. Acids Res. 9*:731; US patent 4,738,921; EP-A-0036776 and EP-A-0121775]. The g-laotamase (*bla*) promoter system [Weissmann (1981) "The cloning of interferon and other mistakes."

In *Interferon 3* (ed. I. Gresser)], bacteriophage lambda PL [Shimatake *et al.* (1981) *Nature 292*:128] and T5 [US patent 4,689,406] promoter systems also provide useful promoter sequences.

In addition, synthetic promoters which do not occur in nature also function as bacterial promoters. For example, transcription activation sequences of one bacterial or bacteriophage promoter may be joined with the operon sequences of another bacterial or bacteriophage promoter, creating a synthetic hybrid promoter [US patent 4,551,433]. For example, the *tac* promoter is a hybrid *trp-lac* promoter comprised of both *trp* promoter and *lac* operon sequences that is regulated by the *lac* repressor [Amann *et al.* (1983) *Gene 25*:167; de Boer *et al.* (1983) *Proc. Natl. Acad. Sci. 80*:21]. Furthermore, a bacterial promoter can include naturally occurring promoters of non-bacterial origin that have the ability to bind bacterial RNA polymerase and initiate transcription. A naturally occurring promoter of non-bacterial origin can also be coupled with a compatible RNA polymerase to produce high levels of expression of some genes in prokaryotes. The bacteriophage T7 RNA polymerase/promoter system is an example of a coupled promoter system [Studier *et al.* (1986) *J. Mol. Biol. 189*:113; Tabor *et al.* (1985) *Proc Natl. Acad. Sci. 82*:1074]. In addition, a hybrid promoter can also be comprised of a bacteriophage promoter and an *E. coli* operator region (EPO-A-0 267 851).

In addition to a functioning promoter sequence, an efficient ribosome binding site is also useful for the expression of foreign genes in prokaryotes. In *E. coli*, the ribosome binding site is called the Shine-Dalgarno (SD) sequence and includes an initiation codon (ATG) and a sequence 3-9 nucleotides in length located 3-11 nucleotides upstream of the initiation codon [Shine *et al.* (1975) *Nature 254*:34]. The SD sequence is thought to promote binding of mRNA to the ribosome by the pairing of bases between the SD sequence and the 3' and of *E. coli* 16S rRNA [Steitz *et al.* (1979) "Genetic signals and nucleotide sequences in messenger RNA." In *Biological Regulation and Development: Gene Expression* (ed. R.F. Goldberger)]. To express eukaryotic genes and prokaryotic genes with weak ribosome-binding site [Sambrook *et al.* (1989) "Expression of cloned genes in Escherichia coli." In *Molecular Cloning: A Laboratory Manual*].

A DNA molecule may be expressed intracellularly. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus will always be a methionine, which is encoded by the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide or by either *in vivo* on *in vitro* incubation with a bacterial methionine N-terminal peptidase (EPO-A-0 219 237).

Fusion proteins provide an alternative to direct expression. Usually, a DNA sequence encoding the N-terminal portion of an endogenous bacterial protein, or other stable protein, is fused to the 5' end of heterologous coding sequences. Upon expression, this construct will provide a fusion of the two amino acid

sequences. For example, the bacteriophage lambda cell gene can be linked at the 5' terminus of a foreign gene and expressed in bacteria. The resulting fusion protein preferably retains a site for a processing enzyme (factor Xa) to cleave the bacteriophage protein from the foreign gene [Nagai *et al.* (1984) *Nature 309*:810]. Fusion proteins can also be made with sequences from the *lacZ* [Jia *et al.* (1987) *Gene 60*:197], *trpE* [Allen et al. (1987) J. Biotechnol. 5:93; Makoff *et al.* (1989) *J. Gen. Microbiol. 135*:11], and *Chey* [EP-A-0 324 647] genes. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*eg.* ubiquitin specific processing-protease) to cleave the ubiquitin from the foreign protein. Through this method, native foreign protein can be isolated [Miller *et al.* (1989) *Bio/Technology* 7:698].

Alternatively, foreign proteins can also be secreted from the cell by creating chimeric DNA molecules that encode a fusion protein comprised of a signal peptide sequence fragment that provides for secretion of the foreign protein in bacteria [US patent 4,336,336]. The signal sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell. The protein is either secreted into the growth media (gram-positive bacteria) or into the periplasmic space, located between the inner and outer membrane of the cell (gram-negative bacteria). Preferably there are processing sites, which can be cleaved either *in vivo* or *in vitro* encoded between the signal peptide fragment and the foreign gene.

DNA encoding suitable signal sequences can be derived from genes for secreted bacterial proteins, such as the *E. coli* outer membrane protein gene (*ompA*) [Masui *et al.* (1983), in: *Experimental Manipulation of Gene Expression*; Ghrayeb *et al.* (1984) *EMBO J. 3*:2437] and the *E. coli* alkaline phosphatase signal sequence (*phoA*) [Oka *et al.* (1985) *Proc. Natl. Acad. Sci. 82*:7212]. As an additional example, the signal sequence of the alpha-amylase gene from various Bacillus strains can be used to secrete heterologous proteins from *B. subtilis* [Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA 79*:5582; EP-A-0 244 042].

Usually, transcription termination sequences recognized by bacteria are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Transcription termination sequences frequently include DNA sequences of about 50 nucleotides capable of forming stem loop structures that aid in terminating transcription. Examples include transcription termination sequences derived from genes with strong promoters, such as the *trp* gene in *E. coli* as well as other biosynthetic genes.

Usually, the above described components, comprising a promoter, signal sequence (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as bacteria. The replicon will have a replication system, thus allowing it to be maintained in a prokaryotic host either for expression or for cloning and amplification. In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably contain at least about 10, and more preferably at least about 20 plasmids. Either a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host.

Alternatively, the expression constructs can be integrated into the bacterial genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to the bacterial chromosome that allows the vector to integrate. Integrations appear to result from recombinations between homologous DNA in the vector and the bacterial chromosome. For example, integrating vectors constructed with DNA from various Bacillus strains integrate into the Bacillus chromosome (EP-A- 0 127 328). Integrating vectors may also be comprised of bacteriophage or transposon sequences.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of bacterial strains that have been transformed. Selectable markers can be expressed in the bacterial host and may include genes which render bacteria resistant to drugs such as ampicillin, chloramphenicol, erythromycin, kanamycin (neomycin), and tetracycline [Davies *et al.* (1978) *Annu. Rev. Microbiol. 32*:469]. Selectable markers may also include biosynthetic genes, such as those in the histidine, tryptophan, and leucine biosynthetic pathways.

Alternatively, some of the above described components can be put together in transformation vectors. Transformation vectors are usually comprised of a selectable market that is either maintained in a replicon or developed into an integrating vector, as described above.

Expression and transformation vectors, either extra-chromosomal replicons or integrating vectors, have been developed for transformation into many bacteria. For example, expression vectors have been developed for, *inter alia*, the following bacteria: Bacillus subtilis [Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA 79*:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541], Escherichia coli [Shimatake *et al.* (1981) *Nature 292*:128; Amann *et al.* (1985) *Gene 40*:183; Studier *et al.* (1986) *J. Mol. Biol. 189*:113; EP-A-0 036 776,EP-A-0 136 829 and EP-A-0 136 907], Streptococcus cremoris [Powell *et al.* (1988) *Appl.*

Environ. Microbiol. *54*:655]; Streptococcus lividans [Powell *et al.* (1988) *Appl. Environ. Microbiol.* *54*:655], Streptomyces lividans [US patent 4,745,056].

Methods of introducing exogenous DNA into bacterial hosts are well-known in the art, and usually include either the transformation of bacteria treated with $CaCl_2$ or other agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial cells by electroporation. Transformation procedures usually vary with the bacterial species to be transformed. See *eg.* [Masson *et al.* (1989) *FEMS Microbiol. Lett.* *60*:273; Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* *79*:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541, Bacillus], [Miller *et al.* (1988) *Proc. Natl. Acad. Sci.* *85*:856; Wang *et al.* (1990) *J. Bacteriol.* *172*:949, Campylobacter], [Cohen *et al.* (1973) *Proc. Natl. Acad. Sci.* *69*:2110; Dower *et al.* (1988) *Nucleic Acids Res.* *16*:6127; Kushner (1978) "An improved method for transformation of Escherichia coli with ColE1-derived plasmids. In *Genetic Engineering: Proceedings of the International Symposium on Genet(Engineering* (eds. H.W. Boyer and S. Nicosia); Mandel *et al.* (1970) *J. Mol. Biol.* *53*:159; Taketo (1988) *Biochim. Biophys. Acta* *949*:318; Escherichia], [Chassy *et al.* (1987) *FEMS Microbiol. Lett.* *44*:173 Lactobacillus]; [Fiedler *et al.* (1988) *Anal. Biochem* *170*:38, Pseudomonas]; [Augustin *et al.* (1990) *FEMS Microbiol. Lett.* *66*:203, Staphylococcus], [Barany *et al.* (1980) *J. Bacteriol.* *144*:698; Harlander (1987) "Transformation of Streptococcus lactis by electroporation, in: *Streptococcal Genetics* (ed. J. Ferretti and R. Curtiss III); Perry *et al.* (1981) *Infect. Immun.* *32*:1295; Powell *et al.* (1988) *Appl. Environ. Microbiol.* *54*:655; Somkuti *et al.* (1987) *Proc. 4th Evr. Cong. Biotechnology* *1*:412, Streptococcus].

v. Yeast Expression

Yeast expression systems are also known to one of ordinary skill in the art. A yeast promoter is any DNA sequence capable of binding yeast RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*eg.* structural gene) into mRNA. A promoter will have a transcription initiation regio(which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site (the "TATA Box") and a transcription initiation site. A yeast promoter may also have a second domain called an upstream activator sequence (UAS), which, if present, is usually distal to the structural gene. The UAS permits regulated (inducible) expression. Constitutive expression occurs in the absence of a UAS. Regulated expression may be either positive or negative, thereby either enhancing or reducing transcription.

Yeast is a fermenting organism with an active metabolic pathway, therefore sequences encoding enzymes in the metabolic pathway provide particularly useful promoter sequences. Examples include alcohol dehydrogenase (ADH) (EP-A-0 284 044), enolase, glucokinase, glucose-6-phosphate isomerase, glyceraldehyde-3-phosphate-dehydrogenase (GAP or GAPDH), hexokinase, phosphofructokinase, 3-phosphoglycerate mutase, and pyruvate kinase (PyK) (EPO-A-0 329 203). The yeast *PHO5* gene, encoding

acid phosphatase, also provides useful promoter sequences [Myanohara *et al.* (1983) *Proc. Natl. Acad. Sci. USA 80*:1].

In addition, synthetic promoters which do not occur in nature also function as yeast promoters. For example, UAS sequences of one yeast promoter may be joined with the transcription activation region of another yeast promoter, creating a synthetic hybrid promoter. Examples of such hybrid promoters include the ADH regulatory sequence linked to the GAP transcription activation region (US Patent Nos. 4,876,197 and 4,880,734). Other examples of hybrid promoters include promoters which consist of the regulatory sequences of either the *ADH2*, *GAL4*, *GAL10*, OR *PHO5* genes, combined with the transcriptional activation region of a glycolytic enzyme gene such as GAP or PyK (EP-A-0 164 556). Furthermore, a yeast promoter can include naturally occurring promoters of non-yeast origin that have the ability to bind yeast RNA polymerase and initiate transcription. Examples of such promoters include, *inter alia*, [Cohen *et al.* (1980) *Proc. Natl. Acad. Sci. USA 77*:1078; Henikoff *et al.* (1981) *Nature 283*:835; Hollenberg *et al.* (1981) *Curr. Topics Microbiol. Immunol. 96*:119; Hollenberg *et al.* (1979) "The Expression of Bacterial Antibiotic Resistance Genes in the Yeast Saccharomyces cerevisiae," in: *Plasmids of Medical, Environmental and Commercial Importance* (eds. K.N. Timmis and A. Puhler); Mercerau-Puigalon *et al.* (1980) *Gene 11*:163; Panthier *et al.* (1980) *Curr. Genet. 2*:109;].

A DNA molecule may be expressed intracellularly in yeast. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Fusion proteins provide an alternative for yeast expression systems, as well as in mammalian, baculovirus, and bacterial expression systems. Usually, a DNA sequence encoding the N-terminal portion of an endogenous yeast protein, or other stable protein, is fused to the 5' end of heterologous coding sequences. Upon expression, this construct will provide a fusion of the two amino acid sequences. For example, the yeast or human superoxide dismutase (SOD) gene, can be linked at the 5' terminus of a foreign gene and expressed in yeast. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. See *eg.* EP-A-0 196 056. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*eg.* ubiquitin-specific processing protease) to cleave the ubiquitin from the foreign protein. Through this method, therefore, native foreign protein can be isolated (*eg.* WO88/024066).

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provide for

secretion in yeast of the foreign protein. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell.

DNA encoding suitable signal sequences can be derived from genes for secreted yeast proteins, such as the yeast invertase gene (EP-A-0 012 873; JPO. 62,096,086) and the A-factor gene (US patent 4,588,684). Alternatively, leaders of non-yeast origin, such as an interferon leader, exist that also provide for secretion in yeast (EP-A-0 060 057).

A preferred class of secretion leaders are those that employ a fragment of the yeast alpha-factor gene, which contains both a "pre" signal sequence, and a "pro" region. The types of alpha-factor fragments that can be employed include the full-length pre-pro alpha factor leader (about 83 amino acid residues) as well as truncated alpha-factor leaders (usually about 25 to about 50 amino acid residues) (US Patents 4,546,083 and 4,870,008; EP-A-0 324 274). Additional leaders employing an alpha-factor leader fragment that provides for secretion include hybrid alpha-factor leaders made with a presequence of a first yeast, but a pro-region from a second yeast alphafactor. (*eg.* see WO 89/02463.)

Usually, transcription termination sequences recognized by yeast are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Examples of transcription terminator sequence and other yeast-recognized termination sequences, such as those coding for glycolytic enzymes.

Usually, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*eg.* plasmids) capable of stable maintenance in a host, such as yeast or bacteria. The replicon may have two replication systems, thus allowing it to be maintained, for example, in yeast for expression and in a prokaryotic host for cloning and amplification. Examples of such yeast-bacteria shuttle vectors include YEp24 [Botstein *et al.* (1979) *Gene 8*:17-24], pCl/1 [Brake *et al.* (1984) *Proc. Natl. Acad. Sci USA 81*:4642-4646], and YRp17 [Stinchcomb *et al.* (1982) *J. Mol. Biol. 158*:157]. In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably have at least about 10, and more preferably at least about 20. Enter a high or low copy number

vector may be selected, depending upon the effect of the vector and the foreign protein on the host. See *eg.* Brake *et al., supra.*

Alternatively, the expression constructs can be integrated into the yeast genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to a yeast chromosome that allows the vector to integrate, and preferably contain two homologous sequences flanking the expression construct. Integrations appear to result from recombinations between homologous DNA in the vector and the yeast chromosome [Orr-Weaver *et al.* (1983) *Methods in Enzymol. 101*:228-245]. An integrating vector may be directed to a specific locus in yeast by selecting the appropriate homologous sequence for inclusion in the vector. See Orr-Weaver *et al., supra.* One or more expression construct may integrate, possibly affecting levels of recombinant protein produced [Rine *et al.* (1983) *Proc. Natl. Acad. Sci. USA 80*:6750]. The chromosomal sequences included in the vector can occur either as a single segment in the vector, which results in the integration of the entire vector, or two segments homologous to adjacent segments in the chromosome and flanking the expression construct in the vector, which can result in the stable integration of only the expression construct.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of yeast strains that have been transformed. Selectable markers may include biosynthetic genes that can be expressed in the yeast host, such as *ADE2*, *HIS4*, *LEU2*, *TRP1*, and *ALG7*, and the G418 resistance gene, which confer resistance in yeast cells to tunicamycin and G418, respectively. In addition, a suitable selectable marker may also provide yeast with the ability to grow in the presence of toxic compounds, such as metal. For example, the presence of *CUP1* allows yeast to grow in the presence of copper ions [Butt *et al.* (1987) *Microbiol, Rev. 51*:351].

Alternatively, some of the above described components can be put together into transformation vectors. Transformation vectors are usually comprised of a selectable marker that is either maintained in a replicon or developed into an integrating vector, as described above.

Expression and transformation vectors, either extrachromosomal replicons or integrating vectors, have been developed for transformation into many yeasts. For example, expression vectors have been developed for, *inter alia*, the following yeasts:Candida albicans [Kurtz, *et al.* (1986) *Mol. Cell. Biol. 6*:142], Candida maltosa [Kunze, *et al.* (1985) *J. Basic Microbiol. 25*:141]. Hansenula polymorpha [Gleeson, *et al.* (1986) *J. Gen. Microbiol. 132*:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet. 202*:302], Kluyveromyces fragilis [Das, *et al.* (1984) *J. Bacteriol. 158*:1165], Kluyveromyces lactis [De Louvencourt *et al.* (1983) *J. Bacteriol. 154*:737; Van den Berg *et al.* (1990) *Bio/Technology 8*:135], Pichia guillerimondii [Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141], Pichia pastoris [Cregg, *et al.* (1985) *Mol. Cell. Biol. 5*:3376; US Patent

Nos. 4,837,148 and 4,929,555], Saccharomyces cerevisiae [Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA 75*:1929; Ito *et al.* (1983) *J. Bacteriol. 153*:163], Schizosaccharomyces pombe [Beach and Nurse (1981) *Nature 300*:706], and Yarrowia lipolytica [Davidow, *et al.* (1985) *Curr. Genet. 10*:380471 Gaillardin, *et al.* (1985) *Curr. Genet. 10*:49].

Methods of introducing exogenous DNA into yeast hosts are well-known in the art, and usually include either the transformation of spheroplasts or of intact yeast cells treated with alkali cations. Transformation procedures usually vary with the yeast species to be transformed. See *eg.* [Kurtz *et al.* (1986) *Mol. Cell. Biol. 6*:142; Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141; Candida]; [Gleeson *et al.* (1986) *J. Gen. Microbiol. 132*:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet. 202*:302; Hansenula]; [Das *et al.* (1984) *J. Bacteriol. 158*:1165; De Louvencourt *et al.* (1983) *J. Bacteriol. 154*:1165; Van den Berg *et al.* (1990) *Bio/Technology 8*:135; Kluyveromyces]; [Cregg *et al.* (1985) *Mol. Cell. Biol. 5*:3376; Kunze *et al.* (1985) *J. Basic Microbiol. 25*:141; US Patent Nos. 4,837,148 and 4,929,555; Pichia]; [Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA 75*;1929; Ito *et al.* (1983) *J. Bacteriol. 153*:163 Saccharomyces]; [Beach and Nurse (1981) *Nature 300*:706; Schizosaccharomyces]; [Davidow *et al.* (1985) *Curr. Genet. 10*:39; Gaillardin *et al.* (1985) *Curr. Genet. 10*:49; Yarrowia].

Antibodies

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides composed of at least one antibody combining site. An "antibody combining site" is the three-dimensional binding space with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows a binding of the antibody with the antigen. "Antibody" includes, for example, vertebrate antibodies, hybrid antibodies, chimeric antibodies, humanised antibodies, altered antibodies, univalent antibodies, Fab proteins, and single domain antibodies.

Antibodies against the proteins of the invention are useful for affinity chromatography, immunoassays, and distinguishing/identifying Neisserial proteins.

Antibodies to the proteins of the invention, both polyclonal and monoclonal, may be prepared by conventional methods. In general, the protein is first used to immunize a suitable animal, preferably a mouse, rat, rabbit or goat. Rabbits and goats are preferred for the preparation of polyclonal sera due to the volume of serum obtainable, and the availability of labeled anti-rabbit and anti-goat antibodies. Immunization is generally performed by mixing or emulsifying the protein in saline, preferably in an adjuvant such as Freund's complete adjuvant, and injecting the mixture or emulsion parenterally (generally subcutaneously or intramuscularly). A dose of 50-200 μg/injection is typically sufficient. Immunization is generally boosted 2-6 weeks later with one or more injections of the protein in saline, preferably using

Freund's incomplete adjuvant. One may alternatively generate antibodies by in vitro immunization using methods known in the art, which for the purposes of this invention is considered equivalent to *in vivo* immunization. Polyclonal antisera is obtained by bleeding the immunized animal into a glass or plastic container, incubating the blood at 25°C for one hour, followed by incubating at 4°C for 2-18 hours. The serum is recovered by centrifugation (*eg.* 1,000*g* for 10 minutes). About 20-50 ml per bleed may be obtained from rabbits.

Monoclonal antibodies are prepared using the standard method of Kohler & Milstein [*Nature* (1975) 256:495-96], or a modification thereof. Typically, a mouse or rat is immunized as described above. However, rather than bleeding the animal to extract serum, the spleen (and optionally several large lymph nodes) is removed and dissociated into single cells. If desired, the spleen cells may be screened (after removal of nonspecifically adherent cells) by applying a cell suspension to a plate or well coated with the protein antigen. B-cells expressing membrane-bound immunoglobulin specific for the antigen bind to the plate, and are not rinsed away with the rest of the suspension. Resulting B-cells, or all dissociated spleen cells, are then induced to fuse with myeloma cells to form hybridomas, and are cultured in a selective medium (*eg.* hypoxanthine, aminopterin, thymidine medium, "HAT"). The resulting hybridomas are plated by limiting dilution, and are assayed for the production of antibodies which bind specifically to the immunizing antigen (and which do not bind to unrelated antigens). The selected MAb-secreting hybridomas are then cultured either *in vitro* (*eg.* in tissue culture bottles or hollow fiber reactors), or *in vivo* (as ascites in mice).

If desired, the antibodies (whether polyclonal or monoclonal) may be labeled using conventional techniques. Suitable labels include fluorophores, chromophores, radioactive atoms (particularly ^{32}P and ^{125}I), electron-dense reagents, enzymes, and ligands having specific binding partners. Enzymes are typically detected by their activity. For example, horseradish peroxidase is usually detected by its ability to convert 3,3',5,5'-tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. "Specific binding partner" refers to a protein capable of binding a ligand molecule with high specificity, as for example in the case of an antigen and a monoclonal antibody specific therefor. Other specific binding partners include biotin and avidin or streptavidin, IgG and protein A, and the numerous receptor-ligand couples known in the art. It should be understood that the above description is not meant to categorize the various labels into distinct classes, as the same label may serve in several different modes. For example, ^{125}I may serve as a radioactive label or as an electron-dense reagent. HRP may serve as enzyme or as antigen for a MAb. Further, one may combine various labels for desired effect. For example, MAbs and avidin also require labels in the practice of this invention: thus, one might label a MAb with biotin, and detect its presence with avidin labeled with ^{125}I, or with an anti-biotin MAb labeled with HRP. Other permutations

and possibilities will be readily apparent to those of ordinary skill in the art, and are considered as equivalents within the scope of the instant invention.

Pharmaceutical Compositions

Pharmaceutical compositions can comprise either polypeptides, antibodies, or nucleic acid of the invention. The pharmaceutical compositions will comprise a therapeutically effective amount of either polypeptides, antibodies, or polynucleotides of the claimed invention.

The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms, such as decreased body temperature. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation can be determined by routine experimentation and is within the judgement of the clinician.

For purposes of the present invention, an effective dose will be from about 0.01 mg/ kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the DNA constructs in the individual to which it is administered.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which may be administered without undue toxicity. Suitable carriers may be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art.

Pharmaceutically acceptable salts can be used therein, for example, mineral acid salts such as hydrochlorides, hydrobromides, phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in Remington's Pharmaceutical Sciences (Mack Pub. Co., N.J. 1991).

Pharmaceutically acceptable carriers in therapeutic compositions may contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles. Typically, the therapeutic compositions

are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier.

Delivery Methods

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated.

Direct delivery of the compositions will generally be accomplished by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal or transcutaneous applications (*eg.* see WO98/20734), needles, and gene guns or hyposprays. Dosage treatment may be a single dose schedule or a multiple dose schedule.

Vaccines

Vaccines according to the invention may either be prophylactic (*ie.* to prevent infection) or therapeutic (*ie.* to treat disease after infection).

Such vaccines comprise immunising antigen(s), immunogen(s), polypeptide(s), protein(s) or nucleic acid, usually in combination with "pharmaceutically acceptable carriers," which include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Additionally, these carriers may function as immunostimulating agents ("adjuvants"). Furthermore, the antigen or immunogen may be conjugated to a bacterial toxoid, such as a toxoid from diphtheria, tetanus, cholera, *H. pylori*, *etc.* pathogens.

Preferred adjuvants to enhance effectiveness of the composition include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™ (WO 90/14837; Chapter 10 in *Vaccine design: the subunit and adjuvant approach*, eds. Powell & Newman, Plenum Press 1995), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer

such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (3) saponin adjuvants, such as Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (*eg.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (*eg.* gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition. Alum and MF59™ are preferred.

As mentioned above, muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (MTP-PE), *etc.*

The immunogenic compositions (*eg.* the immunising antigen/immunogen/polypeptide/protein/ nucleic acid, pharmaceutically acceptable carrier, and adjuvant) typically will contain diluents, such as water, saline, glycerol, ethanol, etc. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles.

Typically, the immunogenic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation also may be emulsified or encapsulated in liposomes for enhanced adjuvant effect, as discussed above under pharmaceutically acceptable carriers.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of the antigenic or immunogenic polypeptides, as well as any other of the above-mentioned components, as needed. By "immunologically effective amount", it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated (*eg.* nonhuman primate, primate, *etc.*), the capacity of the individual's immune system to synthesize antibodies, the degree of protection desired, the formulation of the vaccine, the treating

doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

The immunogenic compositions are conventionally administered parenterally, *eg.* by injection, either subcutaneously, intramuscularly, or transdermally/transcutaneously (*eg.* WO98/20734). Additional formulations suitable for other modes of administration include oral and pulmonary formulations, suppositories, and transdermal applications. Dosage treatment may be a single dose schedule or a multiple dose schedule. The vaccine may be administered in conjunction with other immunoregulatory agents.

As an alternative to protein-based vaccines, DNA vaccination may be employed [*eg.* Robinson & Torres (1997) *Seminars in Immunology* 9:271-283; Donnelly *et al.* (1997) *Annu Rev Immunol* 15:617-648; see later herein].

Gene Delivery Vehicles

Gene therapy vehicles for delivery of constructs including a coding sequence of a therapeutic of the invention, to be delivered to the mammal for expression in the mammal, can be administered either locally or systemically. These constructs can utilize viral or non-viral vector approaches in *in vivo* or *ex vivo* modality. Expression of such coding sequence can be induced using endogenous mammalian or heterologous promoters. Expression of the coding sequence in vivo can be either constitutive or regulated.

The invention includes gene delivery vehicles capable of expressing the contemplated nucleic acid sequences. The gene delivery vehicle is preferably a viral vector and, more preferably, a retroviral, adenoviral, adeno-associated viral (AAV), herpes viral, or alphavirus vector. The viral vector can also be an astrovirus, coronavirus, orthomyxovirus, papovavirus, paramyxovirus, parvovirus, picornavirus, poxvirus, or togavirus viral vector. See generally, Jolly (1994) *Cancer Gene Therapy* 1:51-64; Kimura (1994) *Human Gene Therapy* 5:845-852; Connelly (1995) *Human Gene Therapy* 6:185-193; and Kaplitt (1994) *Nature Genetics* 6:148-153.

Retroviral vectors are well known in the art and we contemplate that any retroviral gene therapy vector is employable in the invention, including B, C and D type retroviruses, xenotropic retroviruses (for example, NZB-X1, NZB-X2 and NZB9-1 (see O'Neill (1985) *J. Virol.* 53:160) polytropic retroviruses *eg.* MCF and MCF-MLV (see Kelly (1983) *J. Virol.* 45:291), spumaviruses and lentiviruses. See RNA Tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985.

Portions of the retroviral gene therapy vector may be derived from different retroviruses. For example, retrovector LTRs may be derived from a Murine Sarcoma Virus, a tRNA binding site from a Rous Sarcoma

Virus, a packaging signal from a Murine Leukemia Virus, and an origin of second strand synthesis from an Avian Leukosis Virus.

These recombinant retroviral vectors may be used to generate transduction competent retroviral vector particles by introducing them into appropriate packaging cell lines (see US patent 5,591,624). Retrovirus vectors can be constructed for site-specific integration into host cell DNA by incorporation of a chimeric integrase enzyme into the retroviral particle (see WO96/37626). It is preferable that the recombinant viral vector is a replication defective recombinant virus.

Packaging cell lines suitable for use with the above-described retrovirus vectors are well known in the art, are readily prepared (see WO95/30763 and WO92/05266), and can be used to create producer cell lines (also termed vector cell lines or "VCLs") for the production of recombinant vector particles. Preferably, the packaging cell lines are made from human parent cells (*eg.* HT1080 cells) or mink parent cell lines, which eliminates inactivation in human serum.

Preferred retroviruses for the construction of retroviral gene therapy vectors include Avian Leukosis Virus, Bovine Leukemia, Virus, Murine Leukemia Virus, Mink-Cell Focus-Inducing Virus, Murine Sarcoma Virus, Reticuloendotheliosis Virus and Rous Sarcoma Virus. Particularly preferred Murine Leukemia Viruses include 4070A and 1504A (Hartley and Rowe (1976) *J Virol* 19:19-25), Abelson (ATCC No. VR-999), Friend (ATCC No. VR-245), Graffi, Gross (ATCC Nol VR-590), Kirsten, Harvey Sarcoma Virus and Rauscher (ATCC No. VR-998) and Moloney Murine Leukemia Virus (ATCC No. VR-190). Such retroviruses may be obtained from depositories or collections such as the American Type Culture Collection ("ATCC") in Rockville, Maryland or isolated from known sources using commonly available techniques.

Exemplary known retroviral gene therapy vectors employable in this invention include those described in patent applications GB2200651, EP0415731, EP0345242, EP0334301, WO89/02468; WO89/05349, WO89/09271, WO90/02806, WO90/07936, WO94/03622, WO93/25698, WO93/25234, WO93/11230, WO93/10218, WO91/02805, WO91/02825, WO95/07994, US 5,219,740, US 4,405,712, US 4,861,719, US 4,980,289, US 4,777,127, US 5,591,624. See also Vile (1993) *Cancer Res* 53:3860-3864; Vile (1993) *Cancer Res* 53:962-967; Ram (1993) *Cancer Res* 53 (1993) 83-88; Takamiya (1992) *J Neurosci Res* 33:493-503; Baba (1993) *J Neurosurg* 79:729-735; Mann (1983) *Cell* 33:153; Cane (1984) *Proc Natl Acad Sci* 81:6349; and Miller (1990) *Human Gene Therapy* 1.

Human adenoviral gene therapy vectors are also known in the art and employable in this invention. See, for example, Berkner (1988) *Biotechniques* 6:616 and Rosenfeld (1991) *Science* 252:431, and WO93/07283, WO93/06223, and WO93/07282. Exemplary known adenoviral gene therapy vectors employable in this

invention include those described in the above referenced documents and in WO94/12649, WO93/03769, WO93/19191, WO94/28938, WO95/11984, WO95/00655, WO95/27071, WO95/29993, WO95/34671, WO96/05320, WO94/08026, WO94/11506, WO93/06223, WO94/24299, WO95/14102, WO95/24297, WO95/02697, WO94/28152, WO94/24299, WO95/09241, WO95/25807, WO95/05835, WO94/18922 and WO95/09654. Alternatively, administration of DNA linked to killed adenovirus as described in Curiel (1992) *Hum. Gene Ther.* 3:147-154 may be employed. The gene delivery vehicles of the invention also include adenovirus associated virus (AAV) vectors. Leading and preferred examples of such vectors for use in this invention are the AAV-2 based vectors disclosed in Srivastava, WO93/09239. Most preferred AAV vectors comprise the two AAV inverted terminal repeats in which the native D-sequences are modified by substitution of nucleotides, such that at least 5 native nucleotides and up to 18 native nucleotides, preferably at least 10 native nucleotides up to 18 native nucleotides, most preferably 10 native nucleotides are retained and the remaining nucleotides of the D-sequence are deleted or replaced with non-native nucleotides. The native D-sequences of the AAV inverted terminal repeats are sequences of 20 consecutive nucleotides in each AAV inverted terminal repeat (*ie.* there is one sequence at each end) which are not involved in HP formation. The non-native replacement nucleotide may be any nucleotide other than the nucleotide found in the native D-sequence in the same position. Other employable exemplary AAV vectors are pWP-19, pWN-1, both of which are disclosed in Nahreini (1993) *Gene* 124:257-262. Another example of such an AAV vector is psub201 (see Samulski (1987) *J. Virol.* 61:3096). Another exemplary AAV vector is the Double-D ITR vector. Construction of the Double-D ITR vector is disclosed in US Patent 5,478,745. Still other vectors are those disclosed in Carter US Patent 4,797,368 and Muzyczka US Patent 5,139,941, Chartejee US Patent 5,474,935, and Kotin WO94/288157. Yet a further example of an AAV vector employable in this invention is SSV9AFABTKneo, which contains the AFP enhancer and albumin promoter and directs expression predominantly in the liver. Its structure and construction are disclosed in Su (1996) *Human Gene Therapy* 7:463-470. Additional AAV gene therapy vectors are described in US 5,354,678, US 5,173,414, US 5,139,941, and US 5,252,479.

The gene therapy vectors of the invention also include herpes vectors. Leading and preferred examples are herpes simplex virus vectors containing a sequence encoding a thymidine kinase polypeptide such as those disclosed in US 5,288,641 and EP0176170 (Roizman). Additional exemplary herpes simplex virus vectors include HFEM/ICP6-LacZ disclosed in WO95/04139 (Wistar Institute), pHSVlac described in Geller (1988) *Science* 241:1667-1669 and in WO90/09441 and WO92/07945, HSV Us3::pgC-lacZ described in Fink (1992) *Human Gene Therapy* 3:11-19 and HSV 7134, 2 RH 105 and GAL4 described in EP 0453242 (Breakefield), and those deposited with the ATCC as accession numbers ATCC VR-977 and ATCC VR-260.

Also contemplated are alpha virus gene therapy vectors that can be employed in this invention. Preferred alpha virus vectors are Sindbis viruses vectors. Togaviruses, Semliki Forest virus (ATCC VR-67; ATCC VR-1247), Middleberg virus (ATCC VR-370), Ross River virus (ATCC VR-373; ATCC VR-1246), Venezuelan equine encephalitis virus (ATCC VR923; ATCC VR-1250; ATCC VR-1249; ATCC VR-532), and those described in US patents 5,091,309, 5,217,879, and WO92/10578. More particularly, those alpha virus vectors described in US Serial No. 08/405,627, filed March 15, 1995,WO94/21792, WO92/10578, WO95/07994, US 5,091,309 and US 5,217,879 are employable. Such alpha viruses may be obtained from depositories or collections such as the ATCC in Rockville, Maryland or isolated from known sources using commonly available techniques. Preferably, alphavirus vectors with reduced cytotoxicity are used (see USSN 08/679640).

DNA vector systems such as eukaryotic layered expression systems are also useful for expressing the nucleic acids of the invention. See WO95/07994 for a detailed description of eukaryotic layered expression systems. Preferably, the eukaryotic layered expression systems of the invention are derived from alphavirus vectors and most preferably from Sindbis viral vectors.

Other viral vectors suitable for use in the present invention include those derived from poliovirus, for example ATCC VR-58 and those described in Evans, Nature 339 (1989) 385 and Sabin (1973) *J. Biol. Standardization* 1:115; rhinovirus, for example ATCC VR-1110 and those described in Arnold (1990) *J Cell Biochem* L401; pox viruses such as canary pox virus or vaccinia virus, for example ATCC VR-111 and ATCC VR-2010 and those described in Fisher-Hoch (1989) *Proc Natl Acad Sci* 86:317; Flexner (1989) *Ann NY Acad Sci* 569:86, Flexner (1990) *Vaccine* 8:17; in US 4,603,112 and US 4,769,330 and WO89/01973; SV40 virus, for example ATCC VR-305 and those described in Mulligan (1979) *Nature* 277:108 and Madzak (1992) *J Gen Virol* 73:1533; influenza virus, for example ATCC VR-797 and recombinant influenza viruses made employing reverse genetics techniques as described in US 5,166,057 and in Enami (1990) *Proc Natl Acad Sci* 87:3802-3805; Enami & Palese (1991) *J Virol* 65:2711-2713 and Luytjes (1989) *Cell* 59:110, (see also McMichael (1983) *NEJ Med* 309:13, and Yap (1978) *Nature* 273:238 and *Nature* (1979) 277:108); human immunodeficiency virus as described in EP-0386882 and in Buchschacher (1992) *J. Virol.* 66:2731; measles virus, for example ATCC VR-67 and VR-1247 and those described in EP-0440219; Aura virus, for example ATCC VR-368; Bebaru virus, for example ATCC VR-600 and ATCC VR-1240; Cabassou virus, for example ATCC VR-922; Chikungunya virus, for example ATCC VR-64 and ATCC VR-1241; Fort Morgan Virus, for example ATCC VR-924; Getah virus, for example ATCC VR-369 and ATCC VR-1243; Kyzylagach virus, for example ATCC VR-927; Mayaro virus, for example ATCC VR-66; Mucambo virus, for example ATCC VR-580 and ATCC VR-1244; Ndumu virus, for example ATCC VR-371; Pixuna virus, for example ATCC VR-372 and ATCC VR-1245; Tonate virus, for example

ATCC VR-925; Triniti virus, for example ATCC VR-469; Una virus, for example ATCC VR-374; Whataroa virus, for example ATCC VR-926; Y-62-33 virus, for example ATCC VR-375; O'Nyong virus, Eastern encephalitis virus, for example ATCC VR-65 and ATCC VR-1242; Western encephalitis virus, for example ATCC VR-70, ATCC VR-1251, ATCC VR-622 and ATCC VR-1252; and coronavirus, for example ATCC VR-740 and those described in Hamre (1966) *Proc Soc Exp Biol Med* 121:190.

Delivery of the compositions of this invention into cells is not limited to the above mentioned viral vectors. Other delivery methods and media may be employed such as, for example, nucleic acid expression vectors, polycationic condensed DNA linked or unlinked to killed adenovirus alone, for example see US Serial No. 08/366,787, filed December 30, 1994 and Curiel (1992) *Hum Gene Ther* 3:147-154 ligand linked DNA, for example see Wu (1989) *J Biol Chem* 264:16985-16987, eucaryotic cell delivery vehicles cells, for example see US Serial No.08/240,030, filed May 9, 1994, and US Serial No. 08/404,796, deposition of photopolymerized hydrogel materials, hand-held gene transfer particle gun, as described in US Patent 5,149,655, ionizing radiation as described in US5,206,152 and in WO92/11033, nucleic charge neutralization or fusion with cell membranes. Additional approaches are described in Philip (1994) *Mol Cell Biol* 14:2411-2418 and in Woffendin (1994) *Proc Natl Acad Sci* 91:1581-1585.

Particle mediated gene transfer may be employed, for example see US Serial No. 60/023,867. Briefly, the sequence can be inserted into conventional vectors that contain conventional control sequences for high level expression, and then incubated with synthetic gene transfer molecules such as polymeric DNA-binding cations like polylysine, protamine, and albumin, linked to cell targeting ligands such as asialoorosomucoid, as described in Wu & Wu (1987) *J. Biol. Chem.* 262:4429-4432, insulin as described in Hucked (1990) *Biochem Pharmacol* 40:253-263, galactose as described in Plank (1992) *Bioconjugate Chem* 3:533-539, lactose or transferrin.

Naked DNA may also be employed. Exemplary naked DNA introduction methods are described in WO 90/11092 and US 5,580,859. Uptake efficiency may be improved using biodegradable latex beads. DNA coated latex beads are efficiently transported into cells after endocytosis initiation by the beads. The method may be improved further by treatment of the beads to increase hydrophobicity and thereby facilitate disruption of the endosome and release of the DNA into the cytoplasm.

Liposomes that can act as gene delivery vehicles are described in US 5,422,120, WO95/13796, WO94/23697, WO91/14445 and EP-524,968. As described in USSN. 60/023,867, on non-viral delivery, the nucleic acid sequences encoding a polypeptide can be inserted into conventional vectors that contain conventional control sequences for high level expression, and then be incubated with synthetic gene transfer molecules such as polymeric DNA-binding cations like polylysine, protamine, and albumin, linked to cell

targeting ligands such as asialoorosomucoid, insulin, galactose, lactose, or transferrin. Other delivery systems include the use of liposomes to encapsulate DNA comprising the gene under the control of a variety of tissue-specific or ubiquitously-active promoters. Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin *et al* (1994) *Proc. Natl. Acad. Sci. USA* 91(24):11581-11585. Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials. Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun, as described in US 5,149,655; use of ionizing radiation for activating transferred gene, as described in US 5,206,152 and WO92/11033

Exemplary liposome and polycationic gene delivery vehicles are those described in US 5,422,120 and 4,762,915; in WO 95/13796; WO94/23697; and WO91/14445; in EP-0524968; and in Stryer, Biochemistry, pages 236-240 (1975) W.H. Freeman, San Francisco; Szoka (1980) *Biochem Biophys Acta* 600:1; Bayer (1979) *Biochem Biophys Acta* 550:464; Rivnay (1987) *Meth Enzymol* 149:119; Wang (1987) *Proc Natl Acad Sci* 84:7851; Plant (1989) *Anal Biochem* 176:420.

A polynucleotide composition can comprises therapeutically effective amount of a gene therapy vehicle, as the term is defined above. For purposes of the present invention, an effective dose will be from about 0.01 mg/ kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the DNA constructs in the individual to which it is administered.

Delivery Methods

Once formulated, the polynucleotide compositions of the invention can be administered (1) directly to the subject; (2) delivered *ex vivo*, to cells derived from the subject; or (3) *in vitro* for expression of recombinant proteins. The subjects to be treated can be mammals or birds. Also, human subjects can be treated.

Direct delivery of the compositions will generally be accomplished by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal or transcutaneous applications (*eg.* see WO98/20734), needles, and gene guns or hyposprays. Dosage treatment may be a single dose schedule or a multiple dose schedule.

Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art and described in *eg.* WO93/14778. Examples of cells useful in ex vivo applications include, for example, stem cells, particularly hematopoetic, lymph cells, macrophages, dendritic cells, or tumor cells.

Generally, delivery of nucleic acids for both *ex vivo* and *in vitro* applications can be accomplished by the following procedures, for example, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei, all well known in the art.

Polynucleotide and polypeptide pharmaceutical compositions

In addition to the pharmaceutically acceptable carriers and salts described above, the following additional agents can be used with polynucleotide and/or polypeptide compositions.

A.Polypeptides

One example are polypeptides which include, without limitation: asioloorosomucoid (ASOR); transferrin; asialoglycoproteins; antibodies; antibody fragments; ferritin; interleukins; interferons, granulocyte, macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), stem cell factor and erythropoietin. Viral antigens, such as envelope proteins, can also be used. Also, proteins from other invasive organisms, such as the 17 amino acid peptide from the circumsporozoite protein of plasmodium falciparum known as RII.

B.Hormones, Vitamins, *etc.*

Other groups that can be included are, for example: hormones, steroids, androgens, estrogens, thyroid hormone, or vitamins, folic acid.

C.Polyalkylenes, Polysaccharides, *etc.*

Also, polyalkylene glycol can be included with the desired polynucleotides/polypeptides. In a preferred embodiment, the polyalkylene glycol is polyethlylene glycol. In addition, mono-, di-, or polysaccharides can be included. In a preferred embodiment of this aspect, the polysaccharide is dextran or DEAE-dextran. Also, chitosan and poly(lactide-co-glycolide)

D.Lipids, and Liposomes

The desired polynucleotide/polypeptide can also be encapsulated in lipids or packaged in liposomes prior to delivery to the subject or to cells derived therefrom.

Lipid encapsulation is generally accomplished using liposomes which are able to stably bind or entrap and retain nucleic acid. The ratio of condensed polynucleotide to lipid preparation can vary but will generally be around 1:1 (mg DNA:micromoles lipid), or more of lipid. For a review of the use of liposomes as carriers for delivery of nucleic acids, see, Hug and Sleight (1991) *Biochim. Biophys. Acta.* 1097:1-17; Straubinger (1983) *Meth. Enzymol.* 101:512-527.

Liposomal preparations for use in the present invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner (1987) *Proc. Natl. Acad. Sci. USA* 84:7413-7416); mRNA (Malone (1989) *Proc. Natl. Acad. Sci. USA* 86:6077-6081); and purified transcription factors (Debs (1990) *J. Biol. Chem.* 265:10189-10192), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, NY. (See, also, Felgner *supra*). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boerhinger). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, *eg.* Szoka (1978) *Proc. Natl. Acad. Sci. USA* 75:4194-4198; WO90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, AL), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

The liposomes can comprise multilammelar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs). The various liposome-nucleic acid complexes are prepared using methods known in the art. See *eg.* Straubinger (1983) *Meth. Immunol.* 101:512-527; Szoka (1978) *Proc. Natl. Acad. Sci. USA* 75:4194-4198; Papahadjopoulos (1975) *Biochim. Biophys. Acta* 394:483; Wilson (1979) *Cell* 17:77); Deamer & Bangham (1976) *Biochim. Biophys. Acta* 443:629; Ostro (1977) *Biochem. Biophys. Res. Commun.* 76:836; Fraley (1979) *Proc. Natl. Acad. Sci. USA* 76:3348); Enoch & Strittmatter (1979) *Proc. Natl. Acad. Sci. USA* 76:145; Fraley (1980) *J. Biol. Chem.* (1980) 255:10431; Szoka & Papahadjopoulos (1978) *Proc. Natl. Acad. Sci. USA* 75:145; and Schaefer-Ridder (1982) *Science* 215:166.

<u>E.Lipoproteins</u>

In addition, lipoproteins can be included with the polynucleotide/polypeptide to be delivered. Examples of lipoproteins to be utilized include: chylomicrons, HDL, IDL, LDL, and VLDL. Mutants, fragments, or fusions of these proteins can also be used. Also, modifications of naturally occurring lipoproteins can be used, such as acetylated LDL. These lipoproteins can target the delivery of polynucleotides to cells

expressing lipoprotein receptors. Preferably, if lipoproteins are including with the polynucleotide to be delivered, no other targeting ligand is included in the composition.

Naturally occurring lipoproteins comprise a lipid and a protein portion. The protein portion are known as apoproteins. At the present, apoproteins A, B, C, D, and E have been isolated and identified. At least two of these contain several proteins, designated by Roman numerals, AI, AII, AIV; CI, CII, CIII.

A lipoprotein can comprise more than one apoprotein. For example, naturally occurring chylomicrons comprises of A, B, C, and E, over time these lipoproteins lose A and acquire C and E apoproteins. VLDL comprises A, B, C, and E apoproteins, LDL comprises apoprotein B; and HDL comprises apoproteins A, C, and E.

The amino acid of these apoproteins are known and are described in, for example, Breslow (1985) Annu Rev. Biochem 54:699; Law (1986) Adv. Exp Med. Biol. 151:162; Chen (1986) J Biol Chem 261:12918; Kane (1980) Proc Natl Acad Sci USA 77:2465; and Utermann (1984) Hum Genet 65:232.

Lipoproteins contain a variety of lipids including, triglycerides, cholesterol (free and esters), and phospholipids. The composition of the lipids varies in naturally occurring lipoproteins. For example, chylomicrons comprise mainly triglycerides. A more detailed description of the lipid content of naturally occurring lipoproteins can be found, for example, in *Meth. Enzymol.* 128 (1986). The composition of the lipids are chosen to aid in conformation of the apoprotein for receptor binding activity. The composition of lipids can also be chosen to facilitate hydrophobic interaction and association with the polynucleotide binding molecule.

Naturally occurring lipoproteins can be isolated from serum by ultracentrifugation, for instance. Such methods are described in *Meth. Enzymol.* (*supra)*; Pitas (1980) *J. Biochem.* 255:5454-5460 and Mahey (1979) *J Clin. Invest* 64:743-750. Lipoproteins can also be produced by *in vitro* or recombinant methods by expression of the apoprotein genes in a desired host cell. See, for example, Atkinson (1986) *Annu Rev Biophys Chem* 15:403 and Radding (1958) *Biochim Biophys Acta* 30: 443. Lipoproteins can also be purchased from commercial suppliers, such as Biomedical Techniologies, Inc., Stoughton, Massachusetts, USA. Further description of lipoproteins can be found in WO98/06437.

F.Polycationic Agents

Polycationic agents can be included, with or without lipoprotein, in a composition with the desired polynucleotide/polypeptide to be delivered.

Polycationic agents, typically, exhibit a net positive charge at physiological relevant pH and are capable of neutralizing the electrical charge of nucleic acids to facilitate delivery to a desired location. These agents

have both in vitro, ex vivo, and in vivo applications. Polycationic agents can be used to deliver nucleic acids to a living subject either intramuscularly, subcutaneously, etc.

The following are examples of useful polypeptides as polycationic agents: polylysine, polyarginine, polyornithine, and protamine. Other examples include histones, protamines, human serum albumin, DNA binding proteins, non-histone chromosomal proteins, coat proteins from DNA viruses, such as (X174, transcriptional factors also contain domains that bind DNA and therefore may be useful as nucleic aid condensing agents. Briefly, transcriptional factors such as C/CEBP, c-jun, c-fos, AP-1, AP-2, AP-3, CPF, Prot-1, Sp-1, Oct-1, Oct-2, CREP, and TFIID contain basic domains that bind DNA sequences.

Organic polycationic agents include: spermine, spermidine, and purtrescine.

The dimensions and of the physical properties of a polycationic agent can be extrapolated from the list above, to construct other polypeptide polycationic agents or to produce synthetic polycationic agents.

Synthetic polycationic agents which are useful include, for example, DEAE-dextran, polybrene. Lipofectin™, and lipofectAMINE™ are monomers that form polycationic complexes when combined with polynucleotides/polypeptides.

Immunodiagnostic Assays

Neisserial antigens of the invention can be used in immunoassays to detect antibody levels (or, conversely, anti-Neisserial antibodies can be used to detect antigen levels). Immunoassays based on well defined, recombinant antigens can be developed to replace invasive diagnostics methods. Antibodies to Neisserial proteins within biological samples, including for example, blood or serum samples, can be detected. Design of the immunoassays is subject to a great deal of variation, and a variety of these are known in the art. Protocols for the immunoassay may be based, for example, upon competition, or direct reaction, or sandwich type assays. Protocols may also, for example, use solid supports, or may be by immunoprecipitation. Most assays involve the use of labeled antibody or polypeptide; the labels may be, for example, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also known; examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays.

Kits suitable for immunodiagnosis and containing the appropriate labeled reagents are constructed by packaging the appropriate materials, including the compositions of the invention, in suitable containers, along with the remaining reagents and materials (for example, suitable buffers, salt solutions, *etc.*) required for the conduct of the assay, as well as suitable set of assay instructions.

Nucleic Acid Hybridisation

"Hybridization" refers to the association of two nucleic acid sequences to one another by hydrogen bonding. Typically, one sequence will be fixed to a solid support and the other will be free in solution. Then, the two sequences will be placed in contact with one another under conditions that favor hydrogen bonding. Factors that affect this bonding include: the type and volume of solvent; reaction temperature; time of hybridization; agitation; agents to block the non-specific attachment of the liquid phase sequence to the solid support (Denhardt's reagent or BLOTTO); concentration of the sequences; use of compounds to increase the rate of association of sequences (dextran sulfate or polyethylene glycol); and the stringency of the washing conditions following hybridization. See Sambrook *et al.* [*supra*] Volume 2, chapter 9, pages 9.47 to 9.57..

"Stringency" refers to conditions in a hybridization reaction that favor association of very similar sequences over sequences that differ. For example, the combination of temperature and salt concentration should be chosen that is approximately 120 to 200°C below the calculated Tm of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized to the sequence of interest and then washed under conditions of different stringencies. See Sambrook *et al.* at page 9.50.

Variables to consider when performing, for example, a Southern blot are (1) the complexity of the DNA being blotted and (2) the homology between the probe and the sequences being detected. The total amount of the fragment(s) to be studied can vary a magnitude of 10, from 0.1 to 1μg for a plasmid or phage digest to 10^{-9} to 10^{-8} g for a single copy gene in a highly complex eukaryotic genome. For lower complexity polynucleotides, substantially shorter blotting, hybridization, and exposure times, a smaller amount of starting polynucleotides, and lower specific activity of probes can be used. For example, a single-copy yeast gene can be detected with an exposure time of only 1 hour starting with 1 μg of yeast DNA, blotting for two hours, and hybridizing for 4-8 hours with a probe of 10^8 cpm/μg. For a single-copy mammalian gene a conservative approach would start with 10 μg of DNA, blot overnight, and hybridize overnight in the presence of 10% dextran sulfate using a probe of greater than 10^8 cpm/μg, resulting in an exposure time of ~24 hours.

Several factors can affect the melting temperature (Tm) of a DNA-DNA hybrid between the probe and the fragment of interest, and consequently, the appropriate conditions for hybridization and washing. In many cases the probe is not 100% homologous to the fragment. Other commonly encountered variables include the length and total G+C content of the hybridizing sequences and the ionic strength and formamide content of the hybridization buffer. The effects of all of these factors can be approximated by a single equation:

$$Tm = 81 + 16.6(\log_{10}Ci) + 0.4[\%(G + C)] - 0.6(\%formamide) - 600/n - 1.5(\%mismatch).$$

where Ci is the salt concentration (monovalent ions) and *n* is the length of the hybrid in base pairs (slightly modified from Meinkoth & Wahl (1984) *Anal. Biochem.* 138: 267-284).

In designing a hybridization experiment, some factors affecting nucleic acid hybridization can be conveniently altered. The temperature of the hybridization and washes and the salt concentration during the washes are the simplest to adjust. As the temperature of the hybridization increases (*ie.* stringency), it becomes less likely for hybridization to occur between strands that are nonhomologous, and as a result, background decreases. If the radiolabeled probe is not completely homologous with the immobilized fragment (as is frequently the case in gene family and interspecies hybridization experiments), the hybridization temperature must be reduced, and background will increase. The temperature of the washes affects the intensity of the hybridizing band and the degree of background in a similar manner. The stringency of the washes is also increased with decreasing salt concentrations.

In general, convenient hybridization temperatures in the presence of 50% formamide are 42°C for a probe with is 95% to 100% homologous to the target fragment, 37°C for 90% to 95% homology, and 32°C for 85% to 90% homology. For lower homologies, formamide content should be lowered and temperature adjusted accordingly, using the equation above. If the homology between the probe and the target fragment are not known, the simplest approach is to start with both hybridization and wash conditions which are nonstringent. If non-specific bands or high background are observed after autoradiography, the filter can be washed at high stringency and reexposed. If the time required for exposure makes this approach impractical, several hybridization and/or washing stringencies should be tested in parallel.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 to 7 show BOXSHADE-rendered alignments of (1) ORF40 (2) ORF4 (3) 225 (4) 235 (5) 287 (6) 519 (7) 919. Conserved amino acids have a solid background.

Figure 8 shows a phylogenetic tree.

Figure 9A illustrates amino acid sequence variability within *N.meningitidis* for ORF4, ORF40, 225, 235, 287, 519, and 919. These sequences were used to construct the phylogenetic tree shown in Figure 9B.

Figures 10 to 19 show BOXSHADE-rendered alignments of (10) ORF4 (11) ORF40 (12) ORF46 (13) 225 (14) 235 (15) 287 (16) 519 (17) 726 (18) 919 (19) 953.

Figure 20 shows Western blots for ORF4, 225, 235, 519 and 919.

EXAMPLES

Example 1

Example 1 of WO99/36544 discloses the cloning and expression of a Neisserial protein referred to as "ORF40". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, and the complete protein sequences show 83.7% identity over 601 aa overlap.

ORF40 was sequenced for a reference population of 21 strains of *N.meningitidis*:

Identification number	Strain	Reference
Group B		
zn02_1	BZ198	Seiler *et al.*(1996)
zn03_1	NG3/88	Seiler *et al.*(1996)
zn04_1	297-0	Seiler *et al.*(1996)
zn06_1	BZ147	Seiler *et al.*(1996)
zn07_1	BZ169	Seiler *et al.*(1996)
zn08_1	528	Seiler *et al.*(1996)
zn10_1	BZ133	Seiler *et al.*(1996)
zn11_1ass	NGE31	Seiler *et al.*(1996)
zn14_1	NGH38	Seiler *et al.*(1996)
zn16_1	NGH15	Seiler *et al.*(1996)
zn18_1	BZ232	Seiler *et al.*(1996)
zn19_1	BZ83	Seiler *et al.*(1996)
zn20_1	44/76	Seiler *et al.*(1996)
zn21_1	MC58	Virji *et al.* (1992)
Group A		
zn22_1	205900	Chiron SpA
zn23_1	F6124	Chiron SpA
z2491_1	Z2491	Maiden *et al.*(1998)
Group C		
zn24_1	90/18311	Chiron SpA
zn25_1ass	93/4286	Chiron SpA
Others		
zn28_1ass	860800 (group Y)	Maiden *et al.*(1998)
zn29_1ass	E32 (group Z)	Maiden *et al.*(1998)

An alignment of these 21 sequences is shown in Figure 1. Stretches of conserved amino acids are evident. The first 17 amino acids, for instance, are conserved (MNKIYRIIWNSALNAWV), although

the serine at residue 11 is not present in 100% of *Neisseria*. This is followed by an amino acid which is not conserved, which is in turn followed by a stretch of 16 conserved amino acids (VSELTRNHTKRASATV). The C-terminal of the protein consists of 116 conserved amino acids.

The conserved regions identified in this example confirm that fragments of the full-length ORF40 protein are suitable as multi-specific vaccines or diagnostic reagents.

ORF40 was re-sequenced for 31 strains in total, and the sequences were aligned. The results are shown in Figure 11.

Conserved regions of particular interest are:

- MNKIYRIIWNSALNAWV
- VSELTRNHTKRASATV
- TAVLATLL
- TLKAGDNLKIKQ
- FTYSLKKDLTDLTSV
- TEKLSFGANG
- KVNITSDTKGLNFAKETAGTNGD
- TVHLNGIGSTLTDTL
- RAAS(V/I)KDVLNAGWNIKGVK
- NVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGK
- KGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGT
- GTTATVSKDDQGNITV
- YDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSM
- PQFSSVSLGAGADAPTLSVD
- NKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGKSMMAI GGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW.

Example 2

Example 26 of WO99/24578 discloses the cloning and expression of a Neisserial protein referred to as "ORF4". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*. The identity between the sequences at an amino acid level are:

	N.meningitidis A	*N.gonorrhoeae*
N.meningitidis B	99.7% over 287 aa	97.6% over 288 aa

ORF4 was sequenced for a reference population of 32 strains of *Neisseria*:

Identification number	Strain	Reference
Group B		
zv01_4	NG6/88	Seiler *et al.* (1996)
zv02_4	BZ198	Seiler *et al.* (1996)
zv03_4ass	NG3/88	Seiler *et al.* (1996)
zv04_4	297-0	Seiler *et al.* (1996)
zv05_4	1000	Seiler *et al.* (1996)
zv06_4	BZ147	Seiler *et al.* (1996)
zv07_4	BZ169	Seiler *et al.* (1996)
zv08_4	528	Seiler *et al.* (1996)
zv09_4	NGP165	Seiler *et al.* (1996)
zv10_4	BZ133	Seiler *et al.* (1996)
zv11_4	NGE31	Seiler *et al.* (1996)
zv12_4ass	NGF26	Seiler *et al.* (1996)
zv13_4	NGE28	Seiler *et al.* (1996)
zv15_4	SWZ107	Seiler *et al.* (1996)
zv16_4	NGH15	Seiler *et al.* (1996)
zv17_4	NGH36	Seiler *et al.* (1996)
zv18_4	BZ232	Seiler *et al.* (1996)
zv19_4	BZ83	Seiler *et al.* (1996)
zv20_4	44/76	Seiler *et al.* (1996)
zv21_4	MC58	Virji *et al.* (1992)
zv96_4	2996	Chiron SpA
Group A		
zv22_4	205900	Chiron SpA
z2491_4	Z2491	Maiden *et al.*, 1998
Group C		
zv24_4	90/18311	Chiron SpA
zv25_4	93/4286	Chiron SpA
Others		
zv26_4ass	A22 (group W)	Maiden *et al.* (1998)
zv27_4	E26 (group X)	Maiden *et al.* (1998)
zv28_4	860800(group Y)	Maiden *et al.* (1998)
zv29_4	E32 (group Z)	Maiden *et al.* (1998)
N.gonorrhoeae		
zv32_4	Ng F62	Maiden *et al.* (1998)
zv33_4	Ng SN4	R. Moxon

fa1090_4	FA1090	Dempsey *et al.* (1991)

An alignment of the sequences generated using PILEUP is shown in Figure 2. Stretches of conserved amino acids are evident. The first 34 amino acids, for instance, are conserved, although the serine at residue 26 is not present in 100% of *Neisseria*. The C-terminal of the protein consists of 228 conserved amino acids.

The conserved regions identified in this example confirm that fragments of the full-length ORF4 protein are suitable as multi-specific vaccines or diagnostic reagents.

ORF4 was re-sequenced for 35 strains in total, and the sequences were aligned. The results are shown in Figure 10.

Conserved regions of particular interest are:

- MKTFFKTLSAAALALILAACGGQKDSAPAASASAAADNGA
- KKEIVFGTTVGDFGDMVKE
- ELEKKGYTVKLVEFTDYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGK LKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQL PRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNWSAVKTADKDSQWLKDVTEAYNSDAFKAYA HKRFEGYKSPAAWNEGAAK

Example 3

Example 16 of WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "225". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

225 has now been sequenced for a reference population of 34 strains of *Neisseria*:

Identification number	**Strain**	**Source reference**
Group B		
zo01_225	NG6/88	Seiler *et al.*, 1996
zo02_225	BZ198	Seiler *et al.*, 1996
zo03_225	NG3/88	Seiler *et al.*, 1996
zo04_225	297-0	Seiler *et al.*, 1996
zo05_225	1000	Seiler *et al.*, 1996
zo06_225	BZ147	Seiler *et al.*, 1996
zo07_225	BZ169	Seiler *et al.*, 1996
zo08_225	528	Seiler *et al.*, 1996

zo09_225	NGP165	Seiler *et al.*, 1996
zo10_225	BZ133	Seiler *et al.*, 1996
zo11_225	NGE31	Seiler *et al.*, 1996
zo12_225	NGF26	Seiler *et al.*, 1996
zo13_225	NGE28	Seiler *et al.*, 1996
zo14_225	NGH38	Seiler *et al.*, 1996
zo15_225	SWZ107	Seiler *et al.*, 1996
zo16_225	NGH15	Seiler *et al.*, 1996
zo17_225	NGH36	Seiler *et al.*, 1996
zo18_225	BZ232	Seiler *et al.*, 1996
zo19_225	BZ83	Seiler *et al.*, 1996
zo20_225	44/76	Seiler *et al.*, 1996
zo21_225	MC58	Chiron SpA
zo96_225	2996	Chiron SpA
Group A		
zo22_225	205900	Chiron SpA
zo23_225	F6124	Chiron SpA
z2491	Z2491	Maiden *et al.*, 1998
Group C		
zo24_225	90/18311	Chiron SpA
zo25_225	93/4286	Chiron SpA
Others		
zo26_225	A22 (group W)	Maiden *et al.*, 1998
zo27_225	E26 (group X)	Maiden *et al.*, 1998
zo28_225	860800(group Y)	Maiden *et al.*, 1998
zo29_225	E32 (group Z)	Maiden *et al.*, 1998
Gonococcus		
zo32_225	Ng F62	Maiden *et al.*, 1998
zo33_225	Ng SN4	Chiron SpA
fa1090	FA1090	Chiron SpA

An alignment of the sequences generated using PILEUP is shown in Figure 3. Stretches of conserved amino acids are evident. The first 74 amino acids, for instance, are conserved, although the isoleucine at residue 51 is not present in 100% of *Neisseria*. The C-terminal of the protein consists of 148 conserved amino acids. A similar alignment is shown in Figure 13.

The conserved regions identified in this example confirm that fragments of the full-length 225 protein are suitable as multi-specific vaccines or diagnostic reagents.

Example 4

Example 16 of WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "235". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

235 has now been sequenced for a reference population of 31 strains of *Neisseria*:

Identification number	**Strain**	**Reference**
Group B		
gnmzq01	NG6/88	Seiler *et al.*, 1996
gnmzq02	BZ198	Seiler *et al.*, 1996
gnmzq03	NG3/88	Seiler *et al.*, 1996
gnmzq04	1000	Seiler *et al.*, 1996
gnmzq05	1000	Seiler *et al.*, 1996
gnmzq07	BZ169	Seiler *et al.*, 1996
gnmzq08	528	Seiler *et al.*, 1996
gnmzq09	NGP165	Seiler *et al.*, 1996
gnmzq10	BZ133	Seiler *et al.*, 1996
gnmzq11	NGE31	Seiler *et al.*, 1996
gnmzq13	NGE28	Seiler *et al.*, 1996
gnmzq14	NGH38	Seiler *et al.*, 1996
gnmzq15	SWZ107	Seiler *et al.*, 1996
gnmzq16	NGH15	Seiler *et al.*, 1996
gnmzq17	NGH36	Seiler *et al.*, 1996
gnmzq18	BZ232	Seiler *et al.*, 1996
gnmzq19	BZ83	Seiler *et al.*, 1996
gnmzq21	MC58	Virji *et al.*, 1992
Group A		
gnmzq22	205900	Chiron SpA
gnmzq23	F6124	Chiron SpA
z2491	Z2491	Maiden *et al.*, 1998
Group C		
gnmzq24	90/18311	Chiron SpA
gnmzq25	93/4286	Chiron SpA
Others		
gnmzq26	A22 (group W)	Maiden *et al.*, 1998
gnmzq27	E26 (group X)	Maiden *et al.*, 1998

gnmzq28	860800 (group Y)	Maiden *et al.*, 1998
gnmzq29	E32 (group Z)	Maiden *et al.*, 1998
gnmzq31	*N. lactamica*	Chiron SpA
Gonococcus		
gnmzq32	Ng F62	Maiden *et al.*, 1998
gnmzq33	Ng SN4	Chiron SpA
fa1090	FA1090	Dempsey *et al.* 1991

An alignment of the sequences generated using PILEUP is shown in Figure 4. Stretches of conserved amino acids are evident. The protein is wholly conserved, although the serine at residue 168 shows some variance.

The conserved regions identified in this example confirm that fragments of the full-length 235 protein are suitable as multi-specific vaccines or diagnostic reagents.

235 was re-sequenced for 35 strains in total, and the sequences were aligned. The results are shown in Figure 14.

Example 5

Example 16 of WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "287". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

287 has now been sequenced for a reference population of 6 strains of *Neisseria*:

Identification number	Strain	Reference
Group B		
287_2	BZ198	Seiler *et al.*(1996)
287_9	NGP165	Seiler *et al.*(1996)
287_14	NGH38	Seiler *et al.*(1996)
287_21	MC58	Virji *et al.* (1992)
Group A		
z2491	Z2491	Maiden *et al.*(1998)
Gonococcus		
fa1090	FA1090	Dempsey *et al.* (1991)

An alignment of the sequences generated using PILEUP is shown in Figure 5. Stretches of conserved amino acids are evident. The first 42 amino acids, for instance, are well conservedand a long conserved region can be seen at the C-terminus.

The conserved regions identified in this example confirm that fragments of the full-length 287 protein are suitable as multi-specific vaccines or diagnostic reagents.

287 was re-sequenced for 35 strains in total (including C11, a serogroup C *N.meningitidis* strain), and the sequences were aligned. The results are shown in Figure 15.

Conserved regions of particular interest are:

- MFKRSVIAMACI
- ALSACGGGGGGSPDVKSADT
- SKPAAPVV
- QDMAAVS
- ENTGNGGAATTD
- QNDMPQ
- DGPSQNITLTHCK
- KSEFE
- RRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEGNYRYLTYGAEKL
- GGSYAL
- VQGEPAKGEMLAGTAVYNGEVLHFH
- GRFAAKVDFGSKSVDGIIDSGDDLHMG
- QKFKAAIDGNGFKGTWTENGGGDVSG(R/K)FYGPAGEEVAGKYSYRPTDAEKGGFGVFAGKKDRD

Example 6

Example 16 of WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "519". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

519 has now been sequenced for a reference population of 22 strains of *Neisseria*:

Identification number	Strain	Source
Group B		
zv01_519	NG6/88	Seiler *et al.*, 1996
zv02_519	BZ198	Seiler *et al.*, 1996
zv03_519ass	NG3/88	Seiler *et al.*, 1996
zv04_519	297-0	Seiler *et al.*, 1996
zv05_519	1000	Seiler *et al.*, 1996

zv06_519ass	BZ147	Seiler *et al.*, 1996
zv07_519	BZ169	Seiler *et al.*, 1996
zv11_519	NGE31	Seiler *et al.*, 1996
zv12_519	NGF26	Seiler *et al.*, 1996
zv18_519	BZ232	Seiler *et al.*, 1996
zv19_519	BZ83	Seiler *et al.*, 1996
zv20_519ass	44/76	Seiler *et al.*, 1996
zv21_519ass	MC58	Chiron SpA
zv96_519	2996	Chiron SpA
Group A		
zv22_519ass	205900	Chiron SpA
z2491_519	Z2491	Maiden *et al.*, 1998
Others		
zv26_519	A22 (group W)	Maiden *et al.*, 1998
zv27_519	E26 (group X)	Maiden *et al.*, 1998
zv28_519	860800 (group Y)	Maiden *et al.*, 1998
zv29_519ass	E32 (group Z)	Maiden *et al.*, 1998
Gonococcus		
zv32_519	Ng F62	Maiden *et al.*, 1998
fa1090_519	FA1090	Chiron SpA

An alignment of the sequences generated using PILEUP is shown in Figure 6. Stretches of conserved amino acids are evident, and the protein shows conservation along its complete length.

The conserved regions identified in this example confirm that fragments of the full-length 519 protein are suitable as multi-specific vaccines or diagnostic reagents.

519 was re-sequenced for 33 strains in total, and the sequences were aligned. The results are shown in Figure 16.

Conserved regions of particular interest are:

- MEFFIILL
- AVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDN TQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVV
- ALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQ QSEGEAQAAVNASNAEKIARINRAKGEAESLRLVAEANAEANRQIAAALQTQSGADAVNLKIAGQYVT AFKNLAKEDNTRIKPAKVAEIGNPNFRRHEKFSPEAKTAK

Example 7

Example 16 of WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "919". Protein and DNA sequences from serogroup A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

919 has now been sequenced for a reference population of 35 strains of *Neisseria*:

Identification number	**Strains**	**Source**
Group B		
zm01	NG6/88	Seiler *et al.*, 1996
zm02	BZ198	Seiler *et al.*, 1996
zm03	NG3/88	Seiler *et al.*, 1996
zm04	297-0	Seiler *et al.*, 1996
zm05	1000	Seiler *et al.*, 1996
zm06	BZ147	Seiler *et al.*, 1996
zm07	BZ169	Seiler *et al.*, 1996
zm08n	528	Seiler *et al.*, 1996
zm09	NGP165	Seiler *et al.*, 1996
zm10	BZ133	Seiler *et al.*, 1996
zm11asbc	NGE31	Seiler *et al.*, 1996
zm12	NGF26	Seiler *et al.*, 1996
zm13	NGE28	Seiler *et al.*, 1996
zm14	NGH38	Seiler *et al.*, 1996
zm15	SWZ107	Seiler *et al.*, 1996
zm16	NGH15	Seiler *et al.*, 1996
zm17	NGH36	Seiler *et al.*, 1996
zm18	BZ232	Seiler *et al.*, 1996
zm19	BZ83	Seiler *et al.*, 1996
zm20	44/76	Seiler *et al.*, 1996
zm21	MC58	Chiron SpA
zm96	2996	Chiron SpA
Group A		
zm22	205900	Chiron SpA
zm23asbc	F6124	Chiron SpA
z2491	Z2491	Maiden *et al.*, 1998
Group C		
zm24	90/18311	Chiron SpA
zm25	93/4286	Chiron SpA

Others		
zm26	A22 (group W)	Maiden *et al.*, 1998
zm27bc	E26 (group X)	Maiden *et al.*, 1998
zm28	860800 (group Y)	Maiden *et al.*, 1998
zm29asbc	E32 (group Z)	Maiden *et al.*, 1998
zm31asbc	*N. lactamica*	Chiron SpA
Gonococcus		
zm32asbc	Ng F62	Maiden *et al.*, 1998
zm33asbc	Ng SN4	Chiron SpA
fa1090	FA1090	Chiron SpA

An alignment of the sequences generated using PILEUP is shown in Figure 7. Another alignment is shown in Figure 18. Stretches of conserved amino acids are evident. The protein shows almost complete conservation.

The conserved regions identified in this example confirm that fragments of the full-length 919 protein are suitable as multi-specific vaccines or diagnostic reagents.

Conserved regions of particular interest are:

- MKKYLFRAAL
- GIAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTV(G/A)GGGAVYTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDN
- GGTHTADLS
- FPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIG(R/K)YMADKGYLKLGQTSMQGIK
- YMRQNPQRLAEVLGQNPSYIFFREL
- NDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP

Example 8

Example 55 of WO99/23578 discloses the cloning and expression of a Neisserial protein referred to as "ORF46". Protein and DNA sequences from serogroups A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

Full-length ORF46 has been sequenced for a reference population of 6 strains of serogroup B. An alignment of these sequences is shown in Figure 12, from which stretches of conserved amino acids are evident.

Conserved regions of particular interest are:

- RKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAERSGHIGLG
- IQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSPVDGFSLYRIHWDGYEH HPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRSTGQRLADRFHNAG
- MLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGEIVGAGDAVQGISEGSNIAVMHG LGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNPNAAQGIEAVSNIF
- IPIKGIGAVRGKYGLGGITAHP(V/I)KRSQMGEIALPKGKSAVS
- NFADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLANKRHPKTKVPFDGKGFPNFE KDVKY

The conserved regions in ORF46 confirm that fragments of this protein are suitable as multi-specific vaccines or diagnostic reagents.

Example 9

WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "726". Protein and DNA sequences from serogroups A and B *N.meningitidis* are disclosed.

726 has been sequenced for a reference population of 7 *N.meningitidis* strains in serogroups A, B and C. An alignment of these sequences is shown in Figure 17, from which stretches of conserved amino acids are evident.

Conserved regions of particular interest are:

- IYFKNGFYDDTLG
- IPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPS(D/E)YHEWDGKKW
- AAAAARFAEQKTATAFRLA
- KADELKNSLLAGYPQVEIDSFYRQEKEALARQADNNAPTPMLAQIAAARGVELDVLIEKV(I/V)EKS ARLAVAAGAIIGKRQQLEDKLN
- IETAPGLDALEKEIEEWT

The conserved regions in 726 confirm that fragments of this protein are suitable as multi-specific vaccines or diagnostic reagents.

Example 10

WO99/57280 discloses the cloning and expression of a Neisserial protein referred to as "953". Protein and DNA sequences from serogroups A and B *N.meningitidis* are disclosed, along with sequences from *N.gonorrhoeae*.

953 has been sequenced for a reference population of 8 strains of *N.meningitidis* serogroups A, B and C. An alignment of these sequences is shown in Figure 19, from which stretches of conserved amino acids are evident. The protein is well-conserved.

Conserved regions of particular interest are:

- MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIP(I/V)ANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAPVKLKAEKFNCYQSPM
- ATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIP(I/V)ANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAPVKLKAEKFNCYQSPM
- KTEVCGGDFSTTIDRTKWG(M/V)DYLVNVGMTKSVRIDIQIEAAKQ

The conserved regions in 953 confirm that fragments of this protein are suitable as multi-specific vaccines or diagnostic reagents.

Phylogenetic tree

Figure 8 is a dendrogram showing the genetic relationship among 107 *N.meningitidis* strains, based on MLST analysis of six gene fragments [adapted from Maiden *et al.* (1998) *PNAS USA* 95:3140]. The dendrogram can be used to select strains representative of meningococcus serogroup B (arrows). Five additional strains, for which genetic assignment to hypervirulent lineages has been independently determined by Wang *et al.* [*J.Infect.Dis* (1993) 167:1320], Seiler *et al.* [*Mol.Microbiol.* (1996) 19:841], and Virji *et al.* [*Mol.Microbiol.* (1992) 6:1271] are superimposed on the dendrogram and indicated by asterisks. In addition to the 22 strains of MenB, three strains of MenA, two strains of MenC, and one strain each of Men Y, X, Z and W135 were used. These are indicated by bold letters before the name. Where phylogenetic data were not available, the strains are shown outside the tree. The hypervirulent strains ET-5, ET-37 and IV-1 are indicated.

Sequence variability

Figure 9a is a schematic representation of amino acid sequence variability with *N.meningitidis* for proteins 225, 235, 287, 519, 919, ORF4 and ORF40. The horizontal axis represents the sequence of MC58. Amino acid differences within MenB strains are indicated by vertical lines above the horizontal axis; differences within serogroups A, C, Y, X, Z and W135 are indicated by lines below the axis. The height of the vertical lines represents the number of strains with amino acid differences. Peaks thus show variable regions. The bard below 225 and 287 represent sequence segments that are missing from some strains.

Figure 9b is a dendrogram of *N.meningitidis* strains obtained using the same 7 proteins. The phylogenetic analysis based on these genes provided a dendrogram which clusters the hypervirulent strains in agreement with Figure 8. Bars indicate strains which cluster with 100% bootstrap support in agreement with MLST analysis. Numbers at the base of each node are bootstrap scores (only those >80% are reported). Gene sequences from different strains were aligned with the program PILEUP from the GCG package. The phylogenetic analysis was performed using the neighbour-joining algorithm [Saitou & Nei (1987) *Mol.Biol.Evol.* 4:406] as implemented in the NEIGHBOR program of the PHYLIP package. Pairwise distances were calculated using the Kimura-two parameter [Kimura (1980) *J.Mol.Evol.* 16:111] on the 31 *N.meningitidis* strains. The N-terminal region of ORF40, the entire 287, and the tandem repeats of 225 were excluded from the analysis. A total of 1000 bootstrap replicates were allowed to evaluate the level of support. The clustering of the hypervirulent strains was confirmed by maximum parsimony analysis.

Western blots

Antigens ORF4, 225, 235, 519 and 919 were analysed by Western blot for various strains. The results are shown in Figure 20. In the case of 225, the blot shows fragments of different sizes in the different strains, with arrows indicating the band of correct size. 225 contains regions of deletion and insertion of a defined repeat and the size of the fragments on the blots matches the gene variability data.

The strains used for Figure 20 are as follows:

N. meningitidis serogroup B:

1 = NG6/88	2 = BZ198	3 = NG3/88	4 = 297-0	5 = 1000
6 = BZ147	7 = BZ169	8 = 528	9 = NGP165	10 = BZ133
11 = NGE31	12 = NGF26	13 = NGE28	14 = NGH38	15 = SWZ107
16 = NGH15	17 = NGH36	18 = BZ232	19 = BZ83	20 = 44/76
21 = MC58	96 = 2996			

N. meningitidis serogroup A:

22 = 205900   23 = F6124

N. meningitidis serogroup C:

24 = 90/18311   25 = 93/4286

Other *N.meningitidis*

26 = A22 (serogroup W)

27 = E26 (serogroup X)

28 = 860800 (serogroup Y)

29 = E32 (serogroup Z)

Other *Neisseria*

30 = *N. cinerea*

L17 = *N.lactamica*

L19 = *N.lactamica*

31 = *N. gonorrhoeae* F62

32 = *N.gonorrhoeae* SN4

It will be appreciated that the invention has been described by means of example only, and that modifications may be made whilst remaining within the spirit and scope of the invention.

CLAIMS

1. A protein comprising a fragment of a Neisserial protein, wherein said fragment consists of 7 or more consecutive conserved amino acids, provided that said protein is not a full-length Neisserial protein.

2. The protein of claim 1, wherein said fragment consists of 20 or more consecutive conserved amino acids.

3. The protein of claim 1 or claim 2, wherein the conserved amino acids are found in at least 50% or more of a *Neisseria* reference population.

4. The protein of claim 3, wherein the reference population includes a plurality of different *Neisseria* species, preferably *N.meningitidis* and *N.gonorrhoeae*.

5. The protein of claim 4, wherein the reference population includes a plurality of different serogroups of *N.meningitidis*.

6. The protein of claim 3 or claim 4, wherein the reference population comprises: *N.meningitidis* A, strain Z2491; *N.meningitidis* B, strain NG6/88; *N.meningitidis* W, strain A22; and *N.gonorrhoeae*, strain Ng F62.

7. The protein of claim 5, wherein the reference *population* comprises: *N.meningitidis* A, strain Z2491; *N.meningitidis* B, strain NG6/88; and *N.meningitidis* W, strain A22.

8. The protein of any preceding claim, comprising a fragment of a protein disclosed in WO99/24578, WO99/36544, WO99/57280 or WO00/22430.

9. The protein of claim 8, comprising a fragment of one or more of ORF4, ORF40, ORF46, protein 225, protein 235, protein 287, protein 519, protein 726, protein 919 and protein 953.

10. The protein of any one of claims 1 to 7, comprising a fragment of a protein disclosed in Tettelin *et al.* [*Science* (2000) 287:1809-1815].

11. Nucleic acid encoding a protein according to any preceding claim.

12. A protein according to any one of claims 1 to 10, or nucleic acid according to claim 11, for use as a medicament.

13. The use a protein according to any one of claims 1 to 10, or nucleic acid according to claim 11, in the manufacture of a medicament for treating or preventing infection due to Neisserial bacteria.

14. The use a protein according to any one of claims 1 to 10, or nucleic acid according to claim 11, in the manufacture of a multi-specific diagnostic reagent.

15. A protein according to claim 1, comprising one or more of the following amino acid sequences:

MNKIYRIIWNSALNAWV;
VSELTRNHTKRASATV;
TAVLATLL;
TLKAGDNLKIKQ;
FTYSLKKDLTDLTSV;
TEKLSFGANG;
KVNITSDTKGLNFAKETAGTNGD;
TVHLNGIGSTLTDTL;
RAAS(V/I)KDVLNAGWNIKGVK;
NVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGK;
KGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGT;
GTTATVSKDDQGNITV;
YDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSM;
PQFSSVSLGAGADAPTLSVD;
NKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGKSMMAIGGGTY
RGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW.;
MKTFFKTLSAAALALILAACGGQKDSAPAASASAAADNGA;
KKEIVFGTTVGDFGDMVKE;
ELEKKGYTVKLVEFTDYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLE
EVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFA
VVNGNYAISSGMKLTEALFQEPSFAYVNWSAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNE
GAAK;
MFKRSVIAMACI;
ALSACGGGGGGSPDVKSADT;
SKPAAPVV;
QDMAAVS;
ENTGNGGAATTD;
DGPSQNITLTHCK;
RRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEGNYRYLTYGAEKL;
VQGEPAKGEMLAGTAVYNGEVLHFH;
GRFAAKVDFGSKSVDGIIDSGDDLHMG;
QKFKAAIDGNGFKGTWTENGGGDVSG(R/K)FYGPAGEEVAGKYSYRPTDAEKGGFGVFAGKKDRD;
MEFFIILL;
AVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQLTV
DGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVV;

ALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLRLVAEANAEANRQIAAALQTQSGADAVNLKIAGQYVTAFKNLAKEDNTRIKPAKVAEIGNPNFRRHEKFSPEAKTAK;

MKKYLFRAAL;

GIAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTV(G/A)GGGAVYTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDN;

GGTHTADLS;

FPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIG(R/K)YMADKGYLKLGQTSMQGIK;

YMRQNPQRLAEVLGQNPSYIFFREL;

NDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP;

RKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAERSGHIGLG;

IQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSPVDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRSTGQRLADRFHNAG;

MLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGEIVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNPNAAQGIEAVSNIF;

IPIKGIGAVRGKYGLGGITAHP(V/I)KRSQMGEIALPKGKSAVS;

NFADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLANKRHPKTKVPFDGKGFPNFEKDVKY;

IYFKNGFYDDTLG;

IPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPS(D/E)YHEWDGKKW;

AAAAARFAEQKTATAFRLA;

KADELKNSLLAGYPQVEIDSFYRQEKEALARQADNNAPTPMLAQIAAARGVELDVLIEKV(I/V)EKSARLAVAAGAIIGKRQQLEDKLN;

IETAPGLDALEKEIEEWT;

MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIP(I/V)ANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAPVKLKAEKFNCYQSPM;

ATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAKRDGKIDITIP(I/V)ANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNLTMHGKTAPVKLKAEKFNCYQSPM; and

KTEVCGGDFSTTIDRTKWG(M/V)DYLVNVGMTKSVRIDIQIEAAKQ.

FIG. 1A

```
zn07_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASANNEEQEEDL
zn20_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASANNEEQEEDL
zn21_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASANNEEQEEDL
zn06_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQASANNEEQEEDL
zn19_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASANNEEQEEDL
zn03_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVATAVLATLLFATVQASANNEEQEEDL
zn18_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVATAVLATLLFATVQASTT..D.DDDL
zn11_ass  1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQASTT..D.DDDL
zn02_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQASTT..D.DDDL
zn04_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANAT..D.DDDL
zn16_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANAT..D.DDDL
zn14_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANAT..D.DDDL
z2491     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANAT..DEDEEE
zn10_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANATDEDEEEE.
zn22_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANATDEDEEEE.
zn23_1    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANATDEDEEEE.
zn28_ass  1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANATDEDEEEE.
zn24_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANATDTDEDEE.
zn25_ass  1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANATDTDEDEE.
zn08_1    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQANATDTDEDDE.
zn29_ass  1 MNKIYRIIWNIALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANATDEEDNED.
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FIG. 1A(CONTD.)

```
zn07_1     61  YLDPVQRTVAVLIVNSDKEGTGEKEKVEENSDWAVYENEKGVLTAREITLKAGDNLKIKQ
zn20_1     61  YLDPVQRTVAVLIVNSDKEGTGEKEKVEENSDWAVYENEKGVLTAREITLKAGDNLKIKQ
zn21_1     61  YLDPVQRTVAVLIVNSDKEGTGEKEKVEENSDWAVYENEKGVLTAREITLKAGDNLKIKQ
zn06_1     61  YLDPVQRTVAVLIVNSDKEGTGEKEKVEENSDWAVYENEKGVLTAREITLKAGDNLKIKQ
zn19_1     61  YLDPVQRTVAVLIVNSDKEGTGEKEKVEENSDWAVYENEKGVLTAREITLKAGDNLKIKQ
zn03_1     58  YLEPVQRTAPVLSFHADSEGTGEKE.VTEDSNWGVYEDKKGVLTAGTITLKAGDNLKIKQ
zn18_1     58  YLEPVQRTAPVLSFHADSEGTGEKE.VTEDSNWGVYEDKKGVLTAGTITLKAGDNLKIKQ
zn11_ass   58  YLEPVQRTAPVLSFHADSEGTGEKE.VTEDSNWGVYEDKKGVLTAGTITLKAGDNLKIKQ
zn02_1     58  YLEPVQRTAVVLSFRSDKEGTGEKE.GTEDSNWAVYEDEKRVLKAGAITLKAGDNLKIKQ
zn04_1     58  YLEPVQRTAVVLSFRSDKEGTGEKE.GTEDSNWAVYEDEKRVLKAGAITLKAGDNLKIKQ
zn16_1     58  YLEPVQRTAVVLSFRSDKEGTGEKE.GTEDSNWAVYEDEKRVLKAGAITLKAGDNLKIKQ
zn14_1     59  ELEPVVRSALVLQFMIDKEGNGENE.STGNIGWSIYYDNHNTLHGATVTLKAGDNLKIKQ
z2491      60  .LESVQRS.VVGSIQASMEGSGELETISLSMTND...SKEFVDPYIVVTLKAGDNLKIKQ
zn10_1     60  .LESVQRS.VVGSIQASMEGSGELETISLSMTND...SKEFVDPYIVVTLKAGDNLKIKQ
zn22_1     60  .LESVQRS.VVGSIQASMEGSGELETISLSMTND...SKEFVDPYIVVTLKAGDNLKIKQ
zn23_1     60  .LESVQRS.VVGSIQASMEGSGELETISLSMTND...SKEFVDPYIVVTLKAGDNLKIKQ
zn28_ass   60  .LESVQRS.VVGSIQASMEGSGELETISLSMTND...SKEFVDPYIVVTLKAGDNLKIKQ
zn24_1     60  .LESVVRSALVLQFMIDKEGNGEIESTG.DIGWSIYYDDHNTLHGATVTLKAGDNLKIKQ
zn25_ass   60  .LESVVRSALVLQFMIDKEGNGEIESTG.DIGWSIYYDDHNTLHGATVTLKAGDNLKIKQ
zn08_1     60  .LEPVVRSALVLQFMIDKEGNGEIESTG.DIGWSIYYDDHNTLHGATVTLKAGDNLKIKQ
zn29_ass   60  .LEPVVRTAPVLSFHSDKEGTGEKEEVGASSNLTVYEDKNRVLKAGTITLKAGDNLKIKQ
```

FIG. 1A (CONTD.)

zn07_1	121	..........NGTNFTYSLKKDLTDLTSVGTEKLSFSANGNKVNITSDTKGLNFAKETAG
zn20_1	121	..........NGTNFTYSLKKDLTDLTSVGTEKLSFSANGNKVNITSDTKGLNFAKETAG
zn21_1	121	..........NGTNFTYSLKKDLTDLTSVGTEKLSFSANGNKVNITSDTKGLNFAKETAG
zn06_1	121	..........NGTNFTYSLKKDLTDLTSVGTEKLSFSANGNKVNITSDTKGLNFAKETAG
zn19_1	121	..........NGTNFTYSLKKDLTDLTSVGTEKLSFSANGNKVNITSDTKGLNFAKETAG
zn03_1	117	....NTDENTNASSFTYSLKKDLTDLTSVETEKLSFGANGKKVNITSDTKGLNFAKETAG
zn18_1	117	....NTDENTNASSFTYSLKKDLTDLTSVETEKLSFGANGKKVNITSDTKGLNFAKETAG
zn11_ass	117	....NTDENTNASSFTYSLKKDLTDLTSVETEKLSFGANGKKVNITSDTKGLNFAKETAG
zn02_1	117	....NTNENTNDSSFTYSLKKDLTDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
zn04_1	117	....NTNENTNDSSFTYSLKKDLTDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
zn16_1	117	NTNENTNENTNDSSFTYSLKKDLTDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
zn14_1	118	NTNKNTNENTNDSSFTYSLKKDLTDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
z2491	115	....NTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG
zn10_1	115	....NTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG
zn22_1	115	....NTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG
zn23_1	115	....NTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG
zn28_ass	115	....NTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG
zn24_1	118	..........SGKDFTYSLKKELKDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
zn25_ass	118	..........SGKDFTYSLKKELKDLTSVETEKLSFGANGNKVNITSDTKGLNFAKETAG
zn08_1	118	....NTDENTNASSFTYSLKKDLTDLTSVGTEELSFGANGNKVNITSDTKGLNFAKKTAG
zn29_ass	119	NTNENTNENTNASSFTYSLKKDLTGLINVETEKLSFGANGKKVNIISDTKGLNFAKETAG

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FIG. 1B

```
zn07_1    171 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn20_1    171 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn21_1    171 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn06_1    171 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn19_1    171 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn03_1    173 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn18_1    173 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn11_ass  173 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn02_1    173 TNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn04_1    173 TNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn16_1    177 TNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn14_1    178 TNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDKKKRAASVKDVLNAGWNIKGVKP
z2491     171 TNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn10_1    171 TNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn22_1    171 TNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn23_1    171 TNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn28_ass  171 TNGDTTVHLNGIGSTLTDMLLNTGATTNVTNDNVTDDEKKRAASVKDVLNAGWNIKGVKP
zn24_1    168 TNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn25_ass  168 TNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn08_1    174 TNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
zn29_ass  179 TNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNAGWNIKGVKT
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FIG. 1B(CONTD.)

```
zn07_1    231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn20_1    231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn21_1    231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn06_1    231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn19_1    231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn03_1    233 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn18_1    233 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn11_ass  233 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn02_1    233 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn04_1    233 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn16_1    237 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn14_1    238 GTTA..SDNVDFVHTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
z2491     229 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn10_1    229 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn22_1    229 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn23_1    229 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn28_ass  231 GTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKL
zn24_1    226 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn25_ass  226 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn08_1    232 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
zn29_ass  237 GSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKL
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FIG. 1B(CONTD.)

```
zn07_1     289 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn20_1     289 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn21_1     289 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn06_1     289 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn19_1     289 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn03_1     291 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn18_1     291 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
zn11_ass   291 VTGKDKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
zn02_1     291 VTGKGKDENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn04_1     291 VTGKGKDENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn16_1     295 VTGKGKDENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
zn14_1     296 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
z2491      289 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn10_1     289 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn22_1     289 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn23_1     289 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn28_ass   289 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn24_1     286 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
zn25_ass   286 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
zn08_1     292 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNV
zn29_ass   297 VTGKGKGENGSSTDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKV
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FIG. 1C

```
zn07_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn20_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn21_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn06_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn19_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNHLQNSGWDLDSKAVAGSSGKVISGN
zn03_1     351 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn18_1     351 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn11_ass   351 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn02_1     351 TFASGKGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn04_1     351 TFASGKGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn16_1     355 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn14_1     356 TFASGKGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
z2491      349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn10_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn22_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn23_1     349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn28_ass   349 TFASGKGTTATVSKDDQGNITVMYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn24_1     346 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn25_ass   346 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn08_1     352 TFASGKGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
zn29_ass   357 TFASGNGTTATVSKDDQGNITVKYDVNVGDALNVNQLQNSGWNLDSKAVAGSSGKVISGN
```

FIG. 1C(CONTD.)

```
zn07_1     409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDGD.A
zn20_1     409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDGD.A
zn21_1     409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDGD.A
zn06_1     409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDGD.A
zn19_1     409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDGD.A
zn03_1     411 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn18_1     411 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn11_ass   411 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn02_1     411 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn04_1     411 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn16_1     415 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn14_1     416 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDKGA
z2491      409 VSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn10_1     409 VSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn22_1     409 VSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn23_1     409 VSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAPTLSVDDEGA
zn28_ass   409 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDKGA
zn24_1     406 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn25_ass   406 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn08_1     412 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
zn29_ass   417 VSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAPTLSVDDEGA
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FIG. 1C (CONTD.)

zn07_1	468	LNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn20_1	468	LNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn21_1	468	LNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn06_1	468	LNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn19_1	468	LNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn03_1	471	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIAT
zn18_1	471	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIAT
zn11_ass	471	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIAT
zn02_1	471	LNVGSKDTNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn04_1	471	LNVGSKDTNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn16_1	475	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn14_1	476	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
z2491	469	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn10_1	469	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn22_1	469	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn23_1	469	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn28_ass	469	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn24_1	466	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn25_ass	466	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT
zn08_1	472	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIAT
zn29_ass	477	LNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIAT

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FIG. 1D

zn07_1	528	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn20_1	528	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn21_1	528	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn06_1	528	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn19_1	528	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn03_1	531	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn18_1	531	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn11_ass	531	ASLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn02_1	531	AGLVQAYLPGKSMMAIGGDTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn04_1	531	AGLVQAYLPGKSMMAIGGDTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn16_1	535	AGLAQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGASASV
zn14_1	536	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
z2491	529	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn10_1	529	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn22_1	529	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn23_1	529	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn28_ass	529	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn24_1	526	AGLAQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASV
zn25_ass	526	AGLAQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASV
zn08_1	532	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV
zn29_ass	537	AGLVQAYLPGKSMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASV

FIG. 1D(CONTD.)

```
zn07_1     588 GYQW*
zn20_1     588 GYQW*
zn21_1     588 GYQW*
zn06_1     588 GYQW*
zn19_1     588 GYQW*
zn03_1     591 GYQW*
zn18_1     591 GYQW*
zn11_ass   591 GYQW*
zn02_1     591 GYQW*
zn04_1     591 GYQW*
zn16_1     595 GYQW*
zn14_1     596 GYQW*
z2491      589 GYQW*
zn10_1     589 GYQW*
zn22_1     589 GYQW*
zn23_1     589 GYQW*
zn28_ass   589 GYQW*
zn24_1     586 GYQW*
zn25_ass   586 GYQW*
zn08_1     592 GYQW*
zn29_ass   597 GYQW*
```

FIG. 2A

```
fa1090_4   1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVG
zv32_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVG
zv33_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVG
zv02_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv15_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv03_4ass  1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv04_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv05_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv09_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv16_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv18_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv26_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv28_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv08_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv10_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv25_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv17_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv96_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv06_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
zv19_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv20_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
z2491_4    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv13_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv27_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv01_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv07_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv21_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv11_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv29_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv22_4     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVG
zv12_4ass  1 MKTFFKTLSAAALALILAACGGQKDRAPAASASA.ASENGAAKKEILFGTTVG
zv24_4ass  1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVG
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FIG. 2A(CONTD.)

```
fa1090_4   61 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv32_4     61 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv33_4     61 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv02_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv15_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv03_4ass  60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv04_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv05_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv09_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv16_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv18_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv26_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv28_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv08_4     60 EHIQPELEKKGYTVELVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv10_4     60 EHIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv25_4     60 EQIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv17_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv96_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv06_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv19_4     60 EQIQAELEKKGYTVELVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv20_4     60 EQIQAELEKKGYTVELVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
z2491_4    60 EQIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv13_4     60 EQIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv27_4     60 EQIQPELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv01_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv07_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv21_4     60 EQIQAELEKKGYTVKLVEFTDYVVRPNLALAEGELDINVFQHKPYLDDFKKEHN
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zv11_4     60 EQIQVELEKKGYTVKLVEFTDYVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv29_4     60 EQIQVELEKKGYTVKLVEFTDYVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv22_4     60 EQIQPELEKKGYTVELVEFTDYVRPNLALGEGELDINVFQHKPYLDDFKKEHN
zv12_4ass  60 EQIQAELEKKGYTVKLVEFTDYVRPNLALAEGELDINVFQHKPYLDDFKKEHN
zv24_4ass  60 EHIQPELEKKGYTVELVEFTDDVRPNLALGEGELDIIVFQHKPYLDDFKKEQN
```

FIG. 2B

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fa1090_4	121	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALVMLNELGWIKLKDG
zv32_4	121	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALVMLNELGWIKLKDG
zv33_4	121	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALVMLNELGWIKLKDG
zv02_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv15_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv03_4ass	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv04_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv05_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv09_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv16_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv18_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv26_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv28_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv08_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv10_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv25_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALVMLDELGWIKLKDG
zv17_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv96_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv06_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv19_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv20_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
z2491_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv13_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv27_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv01_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv07_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv21_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv11_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv29_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv22_4	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv12_4ass	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG
zv24_4ass	120	QVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLVMLDELGWIKLKDG

FIG. 2B(CONTD.)

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fa1090_4	181	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv32_4	181	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv33_4	181	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv02_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv15_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv03_4ass	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv04_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv05_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv09_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv16_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv18_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv26_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv28_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv08_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv10_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv25_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv17_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv96_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv06_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv19_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv20_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
z2491_4	180	KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP

FIG. 2B(CONTD.)

```
zv13_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv27_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv01_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv07_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv21_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv11_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv29_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv22_4     180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv12_4ass  180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
zv24_4ass  180 KADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEP
```

FIG. 2C

```
fa1090_4   241 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
zv32_4     241 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
zv33_4     241 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
zv02_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAARNEGAAK*
zv15_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAGNEGAAK*
zv03_4ass  240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv04_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv05_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv09_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv16_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv18_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv26_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv28_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv08_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv10_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv25_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv17_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv96_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv06_4     240 SAVKTAHKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv19_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv20_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
z2491_4    240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv13_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv27_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv01_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv07_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv21_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv11_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv29_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv22_4     240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv12_4ass  240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
zv24_4ass  240 SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
```

FIG. 2C(CONTD.)

FIG. 3A

```
zo05_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo08_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
z2491     1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo11_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo20_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo01_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo09_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo12_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo22_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo23_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo24_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo25_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo26_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo96_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo02_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo04_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo06_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo07_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo10_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo14_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo16_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo17_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo18_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo19_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo21_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo27_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo28_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo29_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo13_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAG
zo03_225  1  MDSFFKPAVWAVLWLMFAVRLALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
zo15_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAG
fa1090    1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAG
zo32_225  1  MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAG
zo33_225  1  MDSFFKPAVWAVLWLMFAVRSALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAG
```

FIG. 3A(CONTD.)

```
zo05_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo08_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
z2491      61 NADELIGSAMGLNEQPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRVPARRAGNA
zo11_225   61 NADELIGSAMGLNEQPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNA
zo20_225   61 NADELIGSAMGLNEQPVLPINRAPARRAGNADELIGSAMGLNEQPVLPVNRVPARRAGNA
zo01_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo09_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo12_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo22_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo23_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo24_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo25_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo26_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo96_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo02_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo04_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo06_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo07_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo10_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo14_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo16_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo17_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo18_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo19_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo21_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo27_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo28_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo29_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo13_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo03_225   61 NADELIGSAMGLNE.............................QPVLPVNRVPARRAGNA
zo15_225   61 NADELIGSAMGLNE..............................................
fa1090     61 NADELIGSAMGLNE..............................................
zo32_225   61 NADELIGSAMGLNE..............................................
zo33_225   61 NADELIGSAMGL................................................
```

FIG. 3B

zo05_225	92	DELIGSAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo08_225	92	DELIGSAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
z2491	121	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo11_225	121	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo20_225	121	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo01_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo09_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo12_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo22_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo23_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo24_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo25_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo26_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo96_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSISTGFDCSGF
zo02_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo04_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo06_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo07_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo10_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo14_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo16_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo17_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo18_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo19_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo21_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo27_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo28_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo29_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo13_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo03_225	92	DELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
zo15_225	75	............QPVLPVNRVPARRAGNADELIGNAMGLLGIAYRYGGTSVSTGFDCSGF
fa1090	75	............QPVLPVNRAPARRAGNADELIGSAMGLLGIAYRYGGTSVSTGFDCSGF
zo32_225	75	............QPVLPVNRAPARRAGNADELIGSAMGLLGIAYRYGGTSVSTGFDCSGF
zo33_225	75	............QPVLPVNRAPARRAGNADELIGSAMGLLGIAYRYGGTSVSTGFDCSGF

FIG. 3B (CONTD.)

```
zo05_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo08_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
z2491     181 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo11_225  181 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo20_225  181 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo01_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo09_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo12_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo22_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo23_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo24_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo25_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo26_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo96_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo02_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo04_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo06_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo07_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo10_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo14_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo16_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo17_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo18_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo19_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo21_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo27_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo28_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo29_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo13_225  152 [illegible]QHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo03_225  152 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo15_225  123 MQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
fa1090    123 MQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo32_225  123 MQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
zo33_225  123 MQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
```

FIG. 3C

zo05_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo08_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
z2491	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo11_225	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo20_225	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo01_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo09_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo12_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo22_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo23_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo24_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo25_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo26_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo96_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo02_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo04_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo06_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo07_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo10_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo14_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo16_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo17_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo18_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo19_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo21_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo27_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo28_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo29_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo13_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo03_225	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo15_225	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
fa1090	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo32_225	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN	*
zo33_225	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRIKKNDPSRFLN	*

FIG. 4A

gnmzq09	1	MKPLILGLAAALVLSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGMLAST
gnmzq31	1	MKPLILGLAAVLALSACQVQKAPDFDYTAFKESKPASILVVPPLNESPDVNGTWGMLAST
fa1090	1	MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLAST
gnmzq32	1	MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLAST
gnmzq33	1	MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLAST
gnmzq01	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq05	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq08	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq02	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq03	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq04	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq07	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq10	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq11	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq13	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq15	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq16	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq17	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq19	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq21	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq22	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq23	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq24	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq25	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq27	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq28	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq29	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
z2491	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq14	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq18	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLAST
gnmzq26	1	MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGMLAST

FIG. 4A(CONTD.)

```
gnmzq09  61 AEPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVQPEKLHQIFGNDAVLYITITEYGTS
gnmzq31  61 AEPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITITEYGTS
fa1090   61 AAPISEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq32  61 AAPISEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq33  61 AAPISEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq01  61 AAPLSEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq05  61 AAPLSEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq08  61 AAPLSEAGYYVFPAAVVEETFKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq02  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq03  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq04  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq07  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq10  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq11  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq13  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq15  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq16  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq17  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq19  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq21  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq22  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq23  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq24  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq25  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq27  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq28  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq29  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
z2491    61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq14  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq18  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
gnmzq26  61 AAPLSEAGYYVFPAAVVEETFKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTS
```

FIG. 4B

gnmzq09	121	YQILDSVTTVSARARLVDSRNGKVLWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq31	121	YQILDSVTTVSARARLVDSRNGKVLWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
fa1090	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
gnmzq32	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
gnmzq33	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
gnmzq01	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANNLT
gnmzq05	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANNLT
gnmzq08	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANNLT
gnmzq02	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq03	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq04	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq07	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq10	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq11	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq13	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq15	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq16	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq17	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq19	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq21	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq22	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq23	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq24	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq25	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq27	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq28	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq29	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
z2491	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVSAVVNQIANSLT
gnmzq14	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
gnmzq18	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT
gnmzq26	121	YQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSNSGLLGALVGAVVNQIANSLT

FIG. 4B(CONTD.)

gnmzq09	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq31	181	DRGYQVSKAAAYDLLSPYSHNGILKGPRFVEEQPK*
fa1090	181	DRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
gnmzq32	181	DRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
gnmzq33	181	DRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
gnmzq01	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq05	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq08	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq02	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq03	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq04	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq07	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq10	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq11	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq13	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq15	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq16	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq17	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq19	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq21	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq22	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq23	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq24	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq25	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq27	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq28	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq29	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
z2491	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq14	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq18	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
gnmzq26	181	DRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*

FIG. 5

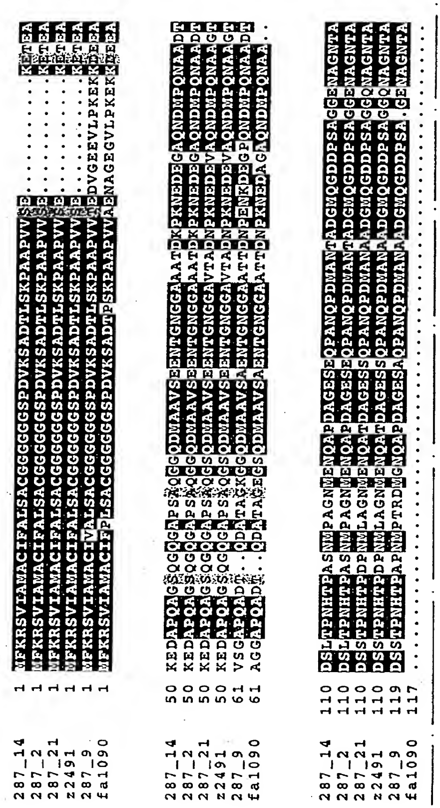

FIG. 5(CONTD.)

```
287_14   170  AQGTNQAENNQTAGSQNPASSTNPSATNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGDS
287_2    170  AQGTNQAENNQTAGSQNPASSTNPSATNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGDS
287_21   170  AQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGDS
z2491    170  AQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGDS
287_9    178  DQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDKV
fa1090   117  .ESANQTGNNQPAGSSDSAPASNPAPANGGSDFGRTNVGNSVVIDGPSQNITLTHCKGDS

287_14   230  CSGNNFLDEEVQLKSEFEKLSDADKISNYKKDGKNDGKNDKFVGLVADSVQMKGINQYII
287_2    230  CSGNNFLDEEVQLKSEFEKLSDADKISNYKKDGKNDGKNDKFVGLVADSVQMKGINQYII
287_21   230  CSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYII
z2491    230  CSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYII
287_9    238  CDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYMI
fa1090   176  CNGDNLLDEEAPSKSEFEKLSDEEKIKRYKK....DEQRENFVGLVADRVKKDGTNKYII

287_14   290  FYKPKP..TSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
287_2    290  FYKPKP..TSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
287_21   286  FYKPKP..TSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
z2491    286  FYKPKP..TSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
287_9    293  IYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
fa1090   232  FYTDKPPT.......RSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPEG
```

FIG. 5(CONTD.)

```
287_14   348  NYRYLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHTENGRPSPSRGRFAA
287_2    348  NYRYLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHTENGRPSPSRGRFAA
287_21   344  NYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFAA
z2491    344  NYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFAA
287_9    353  NYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFAA
fa1090   285  NYRYLTYGAEKLPGGSYALRVQGEPAKGEMLVGTAVYNGEVLHFHMENGRPYPSGGRFAA

287_14   408  KVDFGSKSVDGIIDSGDGLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEVA
287_2    408  KVDFGSKSVDGIIDSGDGLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEVA
287_21   404  KVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEVA
z2491    404  KVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEVA
287_9    413  KVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEVA
fa1090   345  KVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEVA

287_14   468  GKYSYRPTDAEKGGFGVFAGKKEQD*
287_2    468  GKYSYRPTDAEKGGFGVFAGKKEQD*
287_21   464  GKYSYRPTDAEKGGFGVFAGKKEQD*
z2491    464  GKYSYRPTDAEKGGFGVFAGKKEQD*
287_9    473  GKYSYRPTDAEKGGFGVFAGKKEQD*
fa1090   405  GKYSYRPTDAEKGGFGVFAGKKDRD*
```

FIG. 6A

```
z2491_519     1 MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv26_519      1 MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv22_519ass   1 MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
fa1090_519    1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv32_519      1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv11_519      1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv28_519      1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv96_519      1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv02_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv03_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv04_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv05_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv01_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv07_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv12_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv18_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv19_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv21_519ass   1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv27_519      1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv20_519ass   1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv06_519ass   1 MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
zv29_519ass   1 MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSL
```

FIG. 6A (CONTD.)

z2491_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv26_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv22_519ass	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
fa1090_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv32_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv11_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv28_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv96_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv02_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv03_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv04_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv05_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv01_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv07_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv12_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv18_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv19_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv21_519ass	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv27_519	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv20_519ass	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv06_519ass	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG
zv29_519ass	61	KEIPLDVPSQVCITRDNTQLTVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIG

FIG. 6A(CONTD.)

```
z2491_519      121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv26_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv22_519ass    121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
fa1090_519     121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRAMQAQITAERE
zv32_519       121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRAMQAQITAERE
zv11_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv28_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv96_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv02_519       121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv03_519       121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv04_519       121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv05_519       121 RMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv01_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv07_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv12_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv18_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv19_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv21_519ass    121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv27_519       121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv20_519ass    121 RMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
zv06_519ass    121 RMELDKTFEERDEINSTVFSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERK
zv29_519ass    121 RMELDKTFEERDEINSIVVSALDEAAGAWGVKVLRYEIKDLVPPQEILRSMQAQITAERE
```

FIG. 6B

```
z2491_519     181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv26_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv22_519ass   181 KRARIAESEGRKIEQINLASGQREAKIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
fa1090_519    181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv32_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv11_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv28_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv96_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv02_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv03_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv04_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv05_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv01_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv07_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv12_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv18_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv19_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv21_519ass   181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv27_519      181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv20_519ass   181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv06_519ass   181 KRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
zv29_519ass   181 KRARIAESEGRKIEQINLASGQREPEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
```

FIG. 6B (CONTD.)

z2491_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv26_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv22_519ass	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
fa1090_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv32_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv11_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv28_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv96_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv02_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv03_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv04_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv05_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv01_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv07_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv12_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv18_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv19_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv21_519ass	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv27_519	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv20_519ass	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGS[illegible]
zv06_519ass	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL
zv29_519ass	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSL

FIG. 6B (CONTD.)

```
z2491_519     301 ISAGMKIIDSSKTAK*
zv26_519      301 ISAGMKIIDSSKTAK*
zv22_519ass   301 ISAGMKIIDSSKTAK*
fa1090_519    301 ISAGMKIIDSSKTAK*
zv32_519      301 ISAGMKIIDSSKTAK*
zv11_519      301 ISAGMKIIDSSKTAK*
zv28_519      301 ISAGMKIIDSSKTAK*
zv96_519      301 ISAGMKIIDSSKTAK*
zv02_519      301 ISAGMKIIDSSKTAK*
zv03_519      301 ISAGMKIIDSSKTAK*
zv04_519      301 ISAGMKIIDSSKTAK*
zv05_519      301 ISAGMKIIDSSKTAK*
zv01_519      301 ISAGMKIIDSSKTAK*
zv07_519      301 ISAGMKIIDSSKTAK*
zv12_519      301 ISAGMKIIDSSKTAK*
zv18_519      301 ISAGMKIIDSSKTAK*
zv19_519      301 ISAGMKIIDSSKTAK*
zv21_519ass   301 ISAGMKIIDSSKTAK*
zv27_519      301 ISAGMKIIDSSKTAK*
zv20_519ass   301 ISAGMKIIDSSKTAK*
zv06_519ass   301 ISAGMKIIDSSKTAK*
zv29_519ass   301 ISAGMKIIDSNKTAK*
```

FIG. 7A

```
fa1090     1 MKKHLLRSALYGIAAAAILAACQSRSIQTFPQPDTSVINGPDRPAGIPDPAGTTVAGGGAV
zm33asbc   1 MKKHLLRSALYGIAAAAILAACQSRSIQTFPQPDTSVINGPDRPAGIPDPAGTTVAGGGAV
zm32asbc   1 MKKHLLRSALYGIAAAAILAACQSRSIQTFPQPDTSVINGPDRPAGIPDPAGTTVAGGGAV
zm23asbc   1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm27bc     1 MKKYLFRAALYGISAAAILAACQSKSIQTFPQPDTSVINGPDRPAGIPDPAGTTVAGGGAV
zm09       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm10       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm24       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm25       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm14       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm04       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVAGGGAV
zm11asbc   1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPAPAGTTVGGGGAV
zm08n      1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm96       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm01       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm02       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm03       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm07       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm12       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm18       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm19       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm20       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm21       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm06       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm17       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm13       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm05       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
z2491      1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm22       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm26       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm28       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm29asbc   1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDPAGTTVGGGGAV
zm16       1 MKKYLFRAALCGIAAAAILAACQSKSIQTFPQPDTSVINGPGRPVGIPDPAGTTVGGGGAV
zm15       1 MKKYLFRAALYGIAAAAILAACQSKSIQTFPQPDTSVINGPDRPVGIPDLAGTTVGGGGAV
zm31asbc   1 MKKHLFRAALYGIAAAAILAACQSKSIQTFPQPDTSTIKGPDRPAGIPDPAGTTVGGGGAV
```

FIG. 7A(CONTD.)

fa1090	61	YTVVPHLSMPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKRFFER
zm33asbc	61	YTVVPHLSMPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPIHSFQAKRFFER
zm32asbc	61	YTVVPHLSMPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKRFFER
zm23asbc	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm27bc	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm09	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm10	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm24	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm25	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm14	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm04	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm11asbc	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSVQAKQFFER
zm08n	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm96	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm01	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm02	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm03	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm07	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm12	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm18	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm19	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm20	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm21	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm06	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm17	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm13	61	YTVVPHLSLPHWAEQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm05	61	YTVVPHLSLPHWAAQDFAKSLQSFRLSCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
z2491	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSVQAKQFFER
zm22	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSVQAKQFFER
zm26	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSVQAKQFFER
zm28	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm29asbc	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm16	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER
zm15	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNHQGWQDVCAQAFQTPVHSFQAKQFFER
zm31asbc	61	YTVVPHLSLPHWAAQDFAKSLQSFRLGCANLKNRQGWQDVCAQAFQTPVHSFQAKQFFER

FIG. 7B

fa1090	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKN
zm33asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKN
zm32asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKA
zm23asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm27bc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm09	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm10	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm24	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm25	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm14	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm04	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm11asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm08n	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm96	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm01	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm02	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm03	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm07	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm12	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm18	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm19	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm20	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm21	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm06	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm17	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm13	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm05	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
z2491	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm22	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm26	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm28	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm29asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm16	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm15	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA
zm31asbc	121	YFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKA

FIG. 7B(CONTD.)

```
fa1090     181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm33asbc   181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm32asbc   181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm23asbc   181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm27bc     181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm09       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm10       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm24       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm25       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm14       181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm04       181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm11asbc   181 LVRIRQTGKNSGTIDNAGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm08n      181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm96       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm01       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm02       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm03       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm07       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm12       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm18       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm19       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm20       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm21       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm06       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm17       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm13       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm05       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
z2491      181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm22       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm26       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm28       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm29asbc   181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm16       181 LVRIRQTGKNSGTIDNTGGTHTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm15       181 LVRIRQTGKNSGTIDNTGGTHTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGAL
zm31asbc   181 LVRIRQTGKNSGT[illegible]DNAGGTHTADLSRFPITARTTAIKG[illegible]FEGSRFLPYHTRNQINGGAL
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FIG. 7C

fa1090	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm33asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm32asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm23asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm27bc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm09	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm10	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm24	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm25	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm14	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm04	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm11asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm08n	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm96	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm01	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm02	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm03	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm07	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm12	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm18	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm19	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm20	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm21	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm06	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm17	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm13	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm05	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
z2491	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm22	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm26	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm28	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm29asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
zm16	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm15	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
zm31asbc	241	DGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL

FIG. 7C(CONTD.)

```
fa1090     301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSGNEGPVGALGTPLMGEYAGA
zm33asbc   301 KLGQTSMQGIKSYMRQNPHKLAEVLGQNPSYIFFRELAGSGNEGPVGALGTPLMGEYAGA
zm32asbc   301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSGGDGPVGALGTPLMGGYAGA
zm23asbc   301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm27bc     301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm09       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm10       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm24       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm25       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm14       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSRNDGPVGALGTPLMGEYAGA
zm04       301 KLGQTSMQGIKAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm11asbc   301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm08n      301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm96       301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm01       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm02       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm03       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm07       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm12       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm18       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm19       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm20       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm21       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm06       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm17       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm13       301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm05       301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
z2491      301 KLGQTSMQGIKAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm22       301 KLGQTSMQGIKAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm26       301 KLGQTSMQGIKAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm28       301 KLGQTSMQGIKAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGA
zm29asbc   301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm16       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGA
zm15       301 KLGQTSMQGIKSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGA
zm31asbc   301 KLGQTSMQGIKAY[illegible]RQNPQRLAEVLGQNPSYVFFRELAG[illegible]SNDGPVGALGTPLMGEYAGA
```

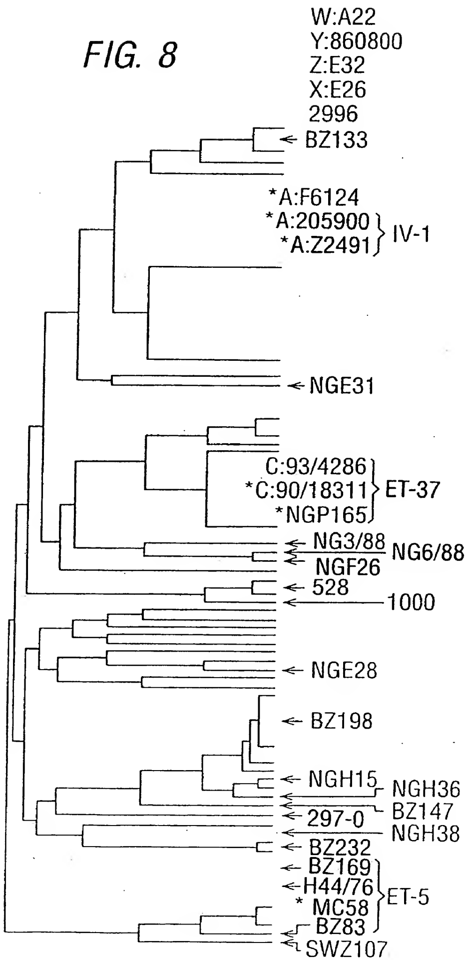
FIG. 7D

fa1090	361	IDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm33asbc	361	IDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm32asbc	361	IDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm23asbc	361	VDRHYITLGAPLFVATAHPVTSKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGETAGK
zm27bc	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGETAGK
zm09	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm10	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm24	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm25	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm14	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm04	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm11asbc	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm08n	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm96	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm01	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm02	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm03	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm07	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm12	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm18	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm19	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm20	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm21	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm06	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm17	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm13	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm05	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
z2491	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm22	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm26	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm28	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm29asbc	361	VDRHYITLGAPLFVATTHPITRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm16	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm15	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK
zm31asbc	361	VDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKGAVRVDYFWGYGDEAGELAGK

FIG. 7D(CONTD.)

fa1090	421	QKTTGYVWQLLPNGMKPEYRP	*
zm33asbc	421	QKTTGYVWQLLPNGMKPEYRP	*
zm32asbc	421	QKTTGYVWQLLPNGMKPEYRP	*
zm23asbc	421	MKEPGYVWQLLPNGMKPEYRP	*
zm27bc	421	MKEPGYVWQLLPNGMKPEYRP	*
zm09	421	QKTTGYVWQLLPNGMKPEYRP	*
zm10	421	QKTTGYVWQLLPNGMKPEYRP	*
zm24	421	QKTTGYVWQLLPNGMKPEYRP	*
zm25	421	QKTTGYVWQLLPNGMKPEYRP	*
zm14	421	QKTTGYVWQLLPNGMKPEYRP	*
zm04	421	QKTTGYVWQLLPNGMKPEYRP	*
zm11asbc	421	QKTTGYVWQLLPNGMKPEYRP	*
zm08n	421	QKTTGYVWQLLPNGMKPEYRP	*
zm96	421	QKTTGYVWQLLPNGMKPEYRP	*
zm01	421	QKTTGYVWQLLPNGMKPEYRP	*
zm02	421	QKTTGYVWQLLPNGMKPEYRP	*
zm03	421	QKTTGYVWQLLPNGMKPEYRP	*
zm07	421	QKTTGYVWQLLPNGMKPEYRP	*
zm12	421	QKTTGYVWQLLPNGMKPEYRP	*
zm18	421	QKTTGYVWQLLPNGMKPEYRP	*
zm19	421	QKTTGYVWQLLPNGMKPEYRP	*
zm20	421	QKTTGYVWQLLPNGMKPEYRP	*
zm21	421	QKTTGYVWQLLPNGMKPEYRP	*
zm06	421	QKTTGYVWQLLPNGMKPEYRP	*
zm17	421	QKTTGYVWQLLPNGMKPEYRP	*
zm13	421	QKTTGYVWQLLPNGMKPEYRP	*
zm05	421	QKTTGYVWQLLPNGMKPEYRP	*
z2491	421	QKTTGYVWQLLPNGMKPEYRP	*
zm22	421	QKTTGYVWQLLPNGMKPEYRP	*
zm26	421	QKTTGYVWQLLPNGMKPEYRP	*
zm28	421	QKTTGYVWQLLPNGMKPEYRP	*
zm29asbc	421	QKTTGYVWQLLPNGMKPEYRP	*
zm16	421	QKTTGYVWQLLPNGMKPEYRP	*
zm15	421	QKTTGYVWQLLPNGMKPEYRP	*
zm31asbc	421	QKTTGYVWQ[illegible]PNGMKPEYRP	*

FIG. 8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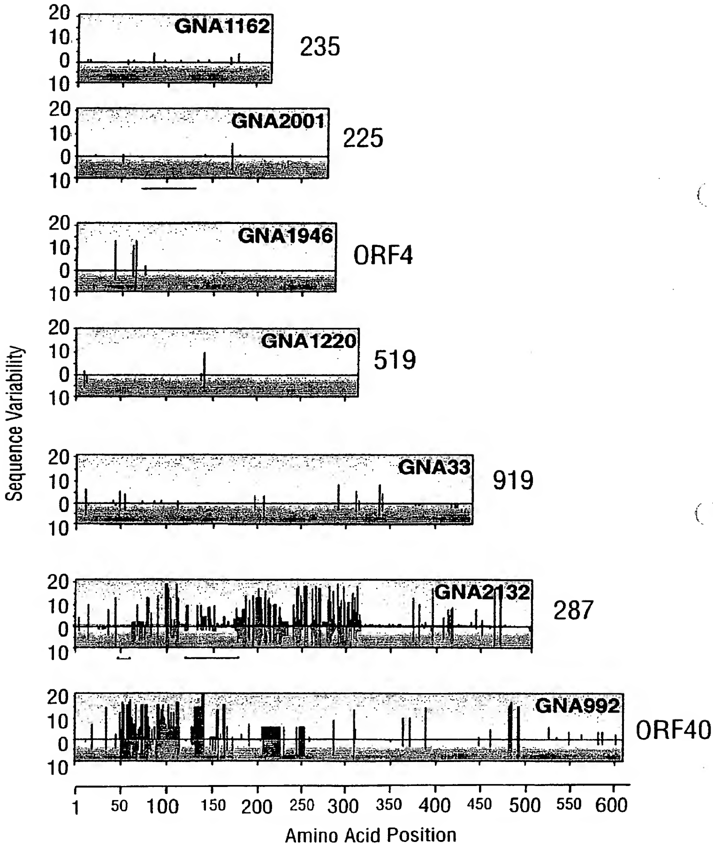
Y:860800
Z:E32
X:E26
2996
BZ133
*A:F6124
*A:205900
*A:Z2491
IV-1
NGE31
C:93/4286
*C:90/18311
*NGP165
ET-37
NG3/88
NG6/88
NGF26
528
1000
NGE28
BZ198
NGH15
NGH36
BZ147
297-0
NGH38
BZ232
BZ169
H44/76
* MC58
ET-5
BZ83
SWZ107

FIG. 9a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GNA2001
225
GNA1946
ORF4
GNA1220
519
GNA33
919
GNA2132
287
GNA992
ORF40
20
10
0
10
1
50
100
150
200
250
300
350
400
450
500
550
600
Amino Acid Position

FIG. 9b

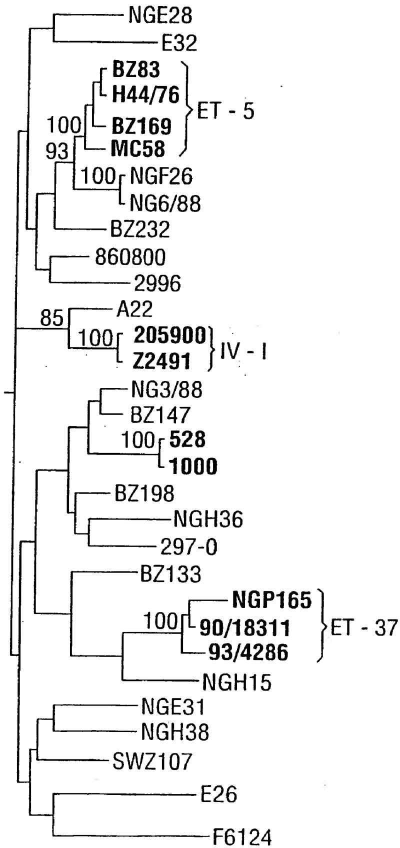
NGE28
E32
BZ83
H44/76
BZ169
MC58
ET - 5
100
93
100
NGF26
NG6/88
BZ232
860800
2996
85
A22
100
205900
Z2491
IV - I
NG3/88
BZ147
100
528
1000
BZ198
NGH36
297-0
BZ133
NGP165
100
90/18311
93/4286
ET - 37
NGH15
NGE31
NGH38
SWZ107
E26
F6124

FIG. 10A

ORF 4

```
BZ147     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
NGH36     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
2996      1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
BZ83      1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVELVEFT
44-76     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVELVEFT
NG6-88    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
BZ169     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
NGF26     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
MC58      1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
NGE31     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQVELEKKGYTVKLVEFT
E32       1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQVELEKKGYTVKLVEFT
NGE28     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVKLVEFT
Z2491     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVKLVEFT
E26       1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVKLVEFT
205900    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVELVEFT
F6124     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVELVEFT
BZ198     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
NG3-88    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
297-0     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
1000      1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
528       1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
NGP165    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
NGH38     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
SWZ107    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
NGH15     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
BZ232     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
90-18311  1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
A22       1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
860800    1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
BZ133     1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEHIQPELEKKGYTVKLVEFT
93-4286   1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAEKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVKLVEFT
Ng-F62    1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
Ng-SN4    1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
FA1090    1 MKTFFKTLSAAALALILAACGGQKDSAPAASAAAPSADNGAAKKEIVFGTTVGDFGDMVKEQIQAELEKKGYTVKLVEFT
N_lactam  1 MKTFFKTLSAAALALILAACGGQKDSAPAASASA.AADNGAAKKEIVFGTTVGDFGDMVKEQIQPELEKKGYTVKLVEFT
```

FIG. 10A(CONTD.)

BZ147	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGH36	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
2996	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
BZ83	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
44-76	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NG6-88	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
BZ169	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGF26	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
MC58	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGE31	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
E32	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGE28	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
Z2491	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
E26	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
205900	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
F6124	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
BZ198	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NG3-88	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
297-0	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
1000	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
528	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGP165	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGH38	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
SWZ107	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
NGH15	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
BZ232	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
90-18311	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
A22	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
860800	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
BZ133	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
93-4286	80	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEVFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARVLV
Ng-F62	81	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEAFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALV
Ng-SN4	81	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEAFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALV
FA1090	81	DYVRPNLALAEGELDINVFQHKPYLDDFKKEHNLDITEAFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALV
N_lactam	80	DYVRPNLALAEGELDINEFQHKPYLDDFKKEHNLDITEAFQVPTAPLGLYPGKLKSLEEVKDGSTVSAPNDPSNFARALV

FIG. 10B

```
BZ147      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGH36      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
2996       160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
BZ83       160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
44-76      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NG6-88     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
BZ169      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGF26      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
MC58       160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGE31      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
E32        160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGE28      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
Z2491      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
E26        160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
205900     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
F6124      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
BZ198      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NG3-88     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
297-0      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
1000       160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
528        160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGP165     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGH38      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
SWZ107     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
NGH15      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
BZ232      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
90-18311   160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
A22        160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
860800     160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
BZ133      160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
93-4286    160 MLDELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
Ng-F62     161 MLNELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
Ng-SN4     161 MLNELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
FA1090     161 MLNELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
N_lactam   160 MLNELGWIKLKDGINPLTASKADIAENLKNIKIVELEAAQLPRSRADVDFAVVNGNYAISSGMKLTEALFQEPSFAYVNW
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FIG. 10B(CONTD.)

BZ147	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGH36	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
2996	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
BZ83	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
44-76	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NG6-88	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
BZ169	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGF26	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
MC58	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGE31	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
E32	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGE28	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
Z2491	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
E26	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
205900	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
F6124	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
BZ198	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NG3-88	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
297-0	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
1000	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
528	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGP165	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGH38	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
SWZ107	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
NGH15	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
BZ232	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
90-18311	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
A22	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
860800	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
BZ133	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
93-4286	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKSPAAWNEGAAK*
Ng-F62	241	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
Ng-SN4	241	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
FA1090	241	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*
N_lactam	240	SAVKTADKDSQWLKDVTEAYNSDAFKAYAHKRFEGYKYPAAWNEGAAK*

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ORF 40

FIG. 11A

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bz169     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASAN....NEEQEEDLYLDPVQRTVAVLIVNS
bz83      1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASAN....NEEQEEDLYLDPVQRTVAVLIVNS
44-76     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASAN....NEEQEEDLYLDPVQRTVAVLIVNS
mc58      1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVKTAVLATLLFATVQASAN....NEEQEEDLYLDPVQRTVAVLIVNS
bz147     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQASAN....NEEQEEDLYLDPVQRTVAVLIVNS
nge28     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLSATVQANAT....DEEDEED..LDPVQRTVAVLIVNS
ng6-88    1 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~MI
ngf26     1 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~MI
ngh38     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELEPVVRSALVLQFMI
ng3-88    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVATAVLATLLFATVQAST.......TDDDDLYLEPVQRTAPVLSFHA
bz232     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVATAVLATLLFATVQAST.......TDDDDLYLEPVQRTAPVLSFHA
nge31     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQAST.......TDDDDLYLEPVQRTAPVLSFHA
ngh15     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANA.......TDDDDLYLEPVQRTAVVLSFRS
2996      1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANA.......TDDDDLYLEPVQRTAVVLSFRS
bz198     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANA.......TDDDDLYLEPVQRTAVVLSFRS
297-0     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANA.......TDDDDLYLEPVQRTAVVLSFRS
ngh36     1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLFATVQANA.......TDDDDLYLEPVQRTAVVLSFRS
e26       1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQASADNVQASADNEEEEYLEPVVRTAPVLSFYS
bz133     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELESVQRS.VVGSIQA
205900    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELESVQRS.VVGSIQA
f6124     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELESVQRS.VVGSIQA
z2491     1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELESVQRS.VVGSIQA
860800    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVKTAVLATLLFATVQANA......TDEDEEEELESVQRS.VVGSIQA
1000      1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQANA......TDTDEDDELEPVVRSALVLQFMI
528       1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVETAVLATLLFATVQANA......TDTDEDDELEPVVRSALVLQFMI
ngp165    1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANA......TDTDEDEELESVVRSALVLQFMI
90-18311  1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANA......TDTDEDEELESVVRSALVLQFMI
93-4286   1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANA......TDTDEDEELESVVRSALVLQFMI
swz107    1 MNKIYRIIWNSALNAWVAVSELTRNHTKRASATVATAVLATLLFATVQAST.......TD.DDDLYLEPVQRTAPVLSFHA
a22       1 MNKIYRIIWNSALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANT......TDEEDEEYLEPVKRTAVVLSFRS
e32       1 MNKIYRIIWNIALNAWVVVSELTRNHTKRASATVATAVLATLLSATVQANA......TDEEDNEDLEPVVRTAPVLSFHS
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FIG. 11A(CONTD.)

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bz169      77 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.REITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
bz83       77 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.REITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
44-76      77 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.REITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
mc58       77 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.REITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
bz147      77 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.REITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
nge28      75 DKEGTGEKEKVEENSDWAVYFNEKGVLTA.GTITLKAGDNLKIKQ..............NGTNFTYSLKKDLTDLTSVGT
ng6-88      3 DKEGNGENE.STGNIGWSIYYDNHNTLHG.ATVTLKAGDNLKIKQNTNK....NTNENTNDSSFTYSLKKDLTDLTSVET
ngf26       3 DKEGNGENE.STGNIGWSIYYDNHNTLHG.ATVTLKAGDNLKIKQNTNKNTNENTNENTNDSSFTYSLKKDLTDLTSVET
ngh38      75 DKEGNGENE.STGNIGWSIYYDNHNTLHG.ATVTLKAGDNLKIKQNTNK....NTNENTNDSSFTYSLKKDLTDLTSVET
ng3-88     74 DSEGTGEKE.VTEDSNWGVYFDKKGVLTA.GTITLKAGDNLKIKQ........NTDENTNASSFTYSLKKDLTDLTSVET
bz232      74 DSEGTGEKE.VTEDSNWGVYFDKKGVLTA.GTITLKAGDNLKIKQ........NTDENTNASSFTYSLKKDLTDLTSVET
nge31      74 DSEGTGEKE.VTEDSNWGVYFDKKGVLTA.GTITLKAGDNLKIKQ........NTDENTNASSFTYSLKKDLTDLTSVET
ngh15      74 DKEGTGEKE.GTEDSNWAVYFDEKRVLKA.GAITLKAGDNLKIKQNTN....ENTNENTNDSSFTYSLKKDLTDLTSVET
2996       74 DKEGTGEKE.GTEDSNWAVYFDEKRVLKA.GAITLKAGDNLKIKQNTN....ENTNENTNDSSFTYSLKKDLTDLTSVET
bz198      74 DKEGTGEKE.GTEDSNWAVYFDEKRVLKA.GAITLKAGDNLKIKQ........NTNENTNDSSFTYSLKKDLTDLTSVET
297-0      74 DKEGTGEKE.GTEDSNWAVYFDEKRVLKA.GAITLKAGDNLKIKQ........NTNENTNDSSFTYSLKKDLTDLTSVET
ngh36      74 DKEGTGEKE.GTEDSNWAVYFDEKRVLKA.GAITLKAGDNLKIKQNTN....ENTNENTNDSSFTYSLKKDLTDLTSVET
e26        81 DAEDTGEKE.VTENTNWGIYFDKNGVIKA.GTITLKAGDNLKIKQ........NTDENTNASSFTYSLKKELTDLTSVGT
bz133      74 SMEGSGELET....ISLSMTNDSKEFVDPYIVVTLKAGDNLKIKQ........NTNENTNASSFTYSLKKDLTGLINVET
205900     74 SMEGSGELET....ISLSMTNDSKEFVDPYIVVTLKAGDNLKIKQ........NTNENTNASSFTYSLKKDLTGLINVET
f6124      74 SMEGSGELET....ISLSMTNDSKEFVDPYIVVTLKAGDNLKIKQ........NTNENTNASSFTYSLKKDLTGLINVET
z2491      74 SMEGSGELET....ISLSMTNDSKEFVDPYIVVTLKAGDNLKIKQ........NTNENTNASSFTYSLKKDLTGLINVET
860800     74 SMEGSGELET....ISLSMTNDSKEFVDPYIVVTLKAGDNLKIKQ........NTNENTNASSFTYSLKKDLTGLINVET
1000       75 DKEGNGEIESTG.DIGWSIYYDDHNTLHG.ATVTLKAGDNLKIKQ........NTDENTNASSFTYSLKKDLTDLTSVGT
528        75 DKEGNGEIESTG.DIGWSIYYDDHNTLHG.ATVTLKAGDNLKIKQ........NTDENTNASSFTYSLKKDLTDLTSVGT
ngp165     75 DKEGNGEIESTG.DIGWSIYYDDHNTLHG.ATVTLKAGDNLKIKQ..............SGKDFTYSLKKELKDLTSVET
90-18311   75 DKEGNGEIESTG.DIGWSIYYDDHNTLHG.ATVTLKAGDNLKIKQ..............SGKDFTYSLKKELKDLTSVET
93-4286    75 DKEGNGEIESTG.DIGWSIYYDDHNTLHG.ATVTLKAGDNLKIKQ..............SGKDFTYSLKKELKDLTSVET
swz107     74 DSEGTGEKEVIG.NTNLGIYFDEKRVLKA.GTITLKAGDNLKIKQNTD....ENTDENTNASSFTYSLKKDLTDLTSVET
a22        75 DKEGTGEKEVTE.DSHWGVYFDEKGVLKA.GTITLKAGDNLKIKQNTD....ENTDENTNASSFTYSLKKDLTDLTSVET
e32        75 DKEGTGEKEEVGASSNLTVYFDKNRVLKA.GTITLKAGDNLKIKQNTN....ENTNENTNASSFTYSLKKDLTGLINVET
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FIG. 11B

bz169	142	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
bz83	142	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
44-76	142	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
mc58	142	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
bz147	142	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
nge28	140	EKLSFSANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
ng6-88	77	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDKKKRAASVKDVLNA
ngf26	81	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDKKKRAASVKDVLNA
ngh38	149	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDKKKRAASVKDVLNA
ng3-88	144	EKLSFGANGKKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
bz232	144	EKLSFGANGKKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
nge31	144	EKLSFGANGKKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
ngh15	148	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
2996	148	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
bz198	144	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
297-0	144	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
ngh36	148	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
e26	151	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
bz133	142	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
205900	142	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
f6124	142	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
z2491	142	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
860800	142	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDMLLNTGATTNVTNDNVTDDEKKRAASVKDVLNA
1000	145	EELSFGANGNKVNITSDTKGLNFAKKTAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
528	145	EELSFGANGNKVNITSDTKGLNFAKKTAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
ngp165	139	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
90-18311	139	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
93-4286	139	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
swz107	148	EKLSFGANGKKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
a22	149	EKLSFGANGNKVNITSDTKGLNFAKETAGTNGDTTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA
e32	150	EKLSFGANGKKVNIISDTKGLNFAKETAGTNGDPTVHLNGIGSTLTDTLAGSSASHVDAGNQST..HYTRAASIKDVLNA

FIG. 11B(CONTD.)

```
bz169     222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
bz83      222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
44-76     222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
mc58      222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
bz147     222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
nge28     220 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
ng6-88    157 GWNIKGVKPGTTA..SDNVDFVHTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
ngf26     161 GWNIKGVKPGTTA..SDNVDFVHTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
ngh38     229 GWNIKGVKPGTTA..SDNVDFVHTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
ng3-88    224 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
bz232     224 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
nge31     224 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
ngh15     228 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKDKGENGS
2996      228 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKDENGS
bz198     224 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
297-0     224 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKDENGS
ngh36     228 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKDENGS
e26       231 GWNIKGVKPGTTA..SDNVDFVHTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKDENGS
bz133     220 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
205900    220 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
f6124     220 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
z2491     220 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
860800    222 GWNIKGVKPGTTA..SDNVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
1000      223 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKKTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
528       223 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
ngp165    217 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
90-18311  217 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
93-4286   217 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
swz107    226 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
a22       227 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
e32       228 GWNIKGVKTGSTTGQSENVDFVRTYDTVEFLSADTKTTTVNVESKDNGKRTEVKIGAKTSVIKEKDGKLVTGKGKGENGS
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FIG. 11C

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bz169     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
bz83      300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
44-76     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
mc58      300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
bz147     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
nge28     298 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
ng6-88    235 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
ngf26     239 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
ngh38     307 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
ng3-88    302 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
bz232     302 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
nge31     302 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
ngh15     306 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
2996      306 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
bz198     302 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
297-0     302 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
ngh36     306 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
e26       309 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQKGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
bz133     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
205900    300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
f6124     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
z2491     300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
860800    300 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
1000      303 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
528       303 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVKYDVNVGDA
ngp165    297 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
90-18311  297 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
93-4286   297 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
swz107    306 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
a22       307 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTNVTFASGKGTTATVSKDDQGNITVMYDVNVGDA
e32       308 STDEGEGLVTAKEVIDAVNKAGWRMKTTTANGQTGQADKFETVTSGTKVTFASGNGTTATVSKDDQGNITVKYDVNVGDA
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FIG. 11C(CONTD.)

bz169	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
bz83	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
44-76	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
mc58	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
bz147	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
nge28	378	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ng6-88	315	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ngf26	319	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ngh38	387	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ng3-88	382	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
bz232	382	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
nge31	382	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ngh15	386	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
2996	386	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
bz198	382	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMAPQFSSVSLGAGADAP
297-0	382	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMAPQFSSVSLGAGADAP
ngh36	386	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMAPQFSSVSLGAGADAP
e26	389	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
bz133	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAP
205900	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAP
f6124	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAP
z2491	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEISRNGKNIDIATSMAPQFSSVSLGAGADAP
860800	380	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
1000	383	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
528	383	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
ngp165	377	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
90-18311	377	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
93-4286	377	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
swz107	386	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
a22	387	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP
e32	388	LNVNQLQNSGWNLDSKAVAGSSGKVISGNVSPSKGKMDETVNINAGNNIEITRNGKNIDIATSMTPQFSSVSLGAGADAP

FIG. 11D

```
bz169      460 TLSVDGD.ALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
bz83       460 TLSVDGD.ALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
44-76      460 TLSVDGD.ALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
mc58       460 TLSVDGD.ALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
bz147      460 TLSVDGD.ALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
nge28      458 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
ng6-88     395 TLSVDG.DALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
ngf26      399 TLSVDG.DALNVGSKKDNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
ngh38      467 TLSVDDKGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
ng3-88     462 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIATAGLVQAYLPGK
bz232      462 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIATAGLVQAYLPGK
nge31      462 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIATAGLVQAYLPGK
ngh15      466 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLAQAYLPGK
2996       466 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLAQAYLPGK
bz198      462 TLSVDDEGALNVGSKDTNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
297-0      462 TLSVDDEGALNVGSKDTNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
ngh36      466 TLSVDDEGALNVGSKDTNKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNALAGIAQAIATAGLVQAYLPGK
e26        469 TLSVDGD.ALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
bz133      460 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
205900     460 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
f6124      460 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
z2491      460 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
860800     460 TLSVDDKGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
1000       463 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIATAGLVQAYLPGK
528        463 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNHIDNVDGNARAGIAQAIATAGLVQAYLPGK
ngp165     457 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLAQAYLPGK
90-18311   457 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLAQAYLPGK
93-4286    457 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLAQAYLPGK
swz107     466 TLSVDDKGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
a22        467 TLSVDDKGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
e32        468 TLSVDDEGALNVGSKDANKPVRITNVAPGVKEGDVTNVAQLKGVAQNLNNRIDNVDGNARAGIAQAIATAGLVQAYLPGK
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bz169	539	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
bz83	539	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
44-76	539	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
mc58	539	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
bz147	539	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
nge28	538	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ng6-88	474	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ngf26	478	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ngh38	547	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ng3-88	542	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
bz232	542	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
nge31	542	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ngh15	546	SMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGASASVGYQW*
2996	546	SMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASVGYQW*
bz198	542	SMMAIGGDTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
297-0	542	SMMAIGGDTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ngh36	546	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
e26	548	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
bz133	540	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
205900	540	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
f6124	540	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
z2491	540	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
860800	540	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
1000	543	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
528	543	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
ngp165	537	SMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASVGYQW*
90-18311	537	SMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASVGYQW*
93-4286	537	SMMAIGGGTYRGEAGYAIGYSSISDTGNWVIKGTASGNSRGHFGTSASVGYQW*
swz107	546	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
a22	547	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*
e32	548	SMMAIGGGTYRGEAGYAIGYSSISDGGNWIIKGTASGNSRGHFGASASVGYQW*

FIG. 11D(CONTD.)

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FIG. 12A

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BZ133     1  LGISRKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER
BZ232     1  ~~~~RKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER
1000      1  ~~~~~KISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER
NGH38     1  LGISRKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER
2996      1  LGISRKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER
MC58      1  LGISRKISLILSILAVCLPMHAHASDLANDSFIRQVLDRQHFEPDGKYHLFGSRGELAER

BZ133    61  SGHIGLGNIQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP
BZ232    57  SGHIGLGKIQSHQLGNLFIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP
1000     56  SGHIGLGNIQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP
NGH38    61  SGHIGLGNIQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP
2996     61  SGHIGLGKIQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP
MC58     61  SGHIGLGKIQSHQLGNLMIQQAAIKGNIGYIVRFSDHGHEVHSPFDNHASHSDSDEAGSP

BZ133   121  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPVPKGARDIYSYDIKGVAQNIRLNLTDNRS
BZ232   117  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRS
1000    116  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRS
NGH38   121  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRS
2996    121  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRS
MC58    121  VDGFSLYRIHWDGYEHHPADGYDGPQGGGYPAPKGARDIYSYDIKGVAQNIRLNLTDNRS
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FIG. 12A(CONTD.)

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BZ133   181  TGQRLADRFHNAGAMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE
BZ232   177  TGQRLADRFHNAGAMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE
1000    176  TGQRLADRFHNAGAMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE
NGH38   181  TGQRLADRFHNAGAMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE
2996    181  TGQRLADRFHNAGSMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE
MC58    181  TGQRLADRFHNAGSMLTQGVGDGFKRATRYSPELDRSGNAAEAFNGTADIVKNIIGAAGE

BZ133   241  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP
BZ232   237  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP
1000    236  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP
NGH38   241  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP
2996    241  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP
MC58    241  IVGAGDAVQGISEGSNIAVMHGLGLLSTENKMARINDLADMAQLKDYAAAAIRDWAVQNP

BZ133   301  NAAQGIEAVSNIFTAVIPIKGIGAVRGKYGLGGITAHPVKRSQMGAIALPKGKSAVSNNF
BZ232   297  NAAQGIEAVSNIFTAVIPVKGIGAVRGKYGLGGITAHPVKRSQMGAIALPKGKSAVSNNF
1000    296  NAAQGIEAVSNIFMAAIPIKGIGAVRGKYGLGGITAHPIKRSQMGAIALPKGKSAVSDNF
NGH38   301  NAAQGIEAVSNIFMAAIPIKGIGAVRGKYGLGGITAHPIKRSQMGAIALPKGKSAVSDNF
2996    301  NAAQGIEAVSNIFMAAIPIKGIGAVRGKYGLGGITAHPIKRSQMGAIALPKGKSAVSDNF
MC58    301  NAAQGIEAVSNIFMAAIPIKGIGAVRGKYGLGGITAHPIKRSQMGAIALPKGKSAVSDNF
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FIG. 12A(CONTD.)

```
BZ133  361  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK
BZ232  357  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK
1000   356  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK
NGH38  361  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK
2996   361  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK
MC58   361  ADAAYAKYPSPYHSRNIRSNLEQRYGKENITSSTVPPSNGKNVKLADQRHPKTGVPFDGK

BZ133  421  GFPNFEKHVKYDTKLDIQELSGGGIPKAKPVFDAKPRWEVDRKLNKLTTREQVEKNVQEI
BZ232  417  GFPNFEKHVKY~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1000   416  GFPNFEKH~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
NGH38  421  GFPNFEKHVKYDTKLDIQELSGGGIPKAKPVSDAKPRWEVDRKLNKLTTREQVEKNVQEI
2996   421  GFPNFEKHVKYDTKLDIQELSGGGIPKAKPVSDAKPRWEVDRKLNKLTTREQVEKNVQEI
MC58   421  GFPNFEKHVKYDTKLDIQELSGGGIPKAKPVFDAKPRWEVDRKLNKLTTREQVEKNVQEI

BZ133  481  RNGNKNSNFSQHAQLEREINKLKSADEINFADGMGKFTDSMNDKAFSRLVKSVKENGFTN
BZ232  428  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1000   424  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
NGH38  481  RNGNKNSNFNQHAQLEREINKLKSADEINFADGMGKFTDSMDDKAFSRLVKSVKENGFTN
2996   481  RNGNKNSNFSQHAQLEREINKLKSADEINFADGMGKFTDSMNDKAFSRLVKSVKENGFTN
MC58   481  RNGNINSNFSQHAQLEREINKLKSADEINFADGMGKFTDSMNDKAFSRLVKSVKENGFTN
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FIG. 12B

```
BZ133   541 PVVEYVEINGKAYIVRGNNRVFAAEYLGRIHELKFKKVDFPVPNTSWKNPTDVLNESGNV
BZ232   428 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1000    424 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
NGH38   541 PVVEYVEINGKAYIVRGNNRVFAAEYLGRIHELKFKKVDFPVPNTSWKNPTDVLNESGNV
2996    541 PVVEYVEINGKAYIVRGNNRVFAAEYLGRIHELKFKKVDFPVPNTSWKNPTDVLNESGNV
MC58    541 PVVEYVEINGKAYIVRGNNRVFAAEYLGRIHELKFKKVDFPVPNTSWKNPTDVLNESGNV

BZ133   601 KRPRYRSK
BZ232   428 ~~~~~~~~
1000    424 ~~~~~~~~
NGH38   601 KRPRYRSK
2996    601 KRPRYRSK
MC58    601 KRPRYRSK
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FIG. 13A

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Ng-F62    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAGNADELIGSAMGLNE......
FA1090    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAGNADELIGSAMGLNE......
1000      1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
528       1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGE31     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNEQPVLPV
Z2491     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNEQPVLPV
44-76     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNEQPVLPI
NG6-88    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGP165    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGF26     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
2996      1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
205900    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
F6124     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
90-18311  1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
93-4286   1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
A22       1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ198     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
297-0     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ147     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ169     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ133     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGH38     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGH15     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGH36     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ232     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
BZ83      1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
MC58      1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
E26       1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
860800    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
E32       1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
NGE28     1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAGNADELIGSAMGLNE......
NG3-88    1 MDSFFKPAVWAVLWLMFAVRLALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
SWZ107    1 MDSFFKPAVWAVLWLMFAVRPALADELTNLLSSREQILRQFAEDEQPVLPINRAPARRAGNADELIGSAMGLNE......
Ng-SN4    1 MDSFFKPAVWAVLWLMFAVRSALADELTNLLSSREQILRQFAEDEQPVLPVNRAPARRAGNADELIGSAMGLNE......
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FIG. 13A(CONTD.)

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Ng-F62    75 ....................................................QPVLPVNRAPARRAGNADELIGSAMGLL
FA1090    75 ....................................................QPVLPVNRAPARRAGNADELIGSAMGLL
1000      75 .......................QPVLPVNRVPARRAGNADELIGSAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
528       75 .......................QPVLPVNRVPARRAGNADELIGSAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGE31     81 NRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
Z2491     81 NRVPARRAGNADELIGNAMGLNEQPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
44-76     81 NRAPARRAGNADELIGSAMGLNEQPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NG6-88    75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGP165    75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGF26     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
2996      75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
205900    75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
F6124     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
90-18311  75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
93-4286   75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
A22       75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ198     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
297-0     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ147     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ169     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ133     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGH38     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGH15     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGH36     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ232     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
BZ83      75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
MC58      75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
E26       75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
860800    75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
E32       75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NGE28     75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
NG3-88    75 .......................QPVLPVNRVPARRAGNADELIGNAMGLNEQPVLPVNRAPARRAGNADELIGNAMGLL
SWZ107    75 ....................................................QPVLPVNRVPARRAGNADELIGNAMGLL
Ng-SN4    75 ....................................................QPVLPVNRAPARRAGNADELIGSAMGLL
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FIG. 13B

Ng-F62	103	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
FA1090	103	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
1000	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
528	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGE31	161	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
Z2491	161	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
44-76	161	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NG6-88	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGP165	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGF26	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
2996	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
205900	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
F6124	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
90-18311	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
93-4286	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
A22	132	GIAYRYGGTSISTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ198	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
297-0	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ147	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ169	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ133	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGH38	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGH15	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGH36	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ232	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
BZ83	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
MC58	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
E26	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
860800	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
E32	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NGE28	132	GIAYRYGGTSVSTGFDCSGFIQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
NG3-88	132	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
SWZ107	103	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGTPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF
Ng-SN4	103	GIAYRYGGTSVSTGFDCSGFMQHIFKRAMGINLPRTSAEQARMGAPVARSELQPGDMVFFRTLGGSRISHVGLYIGNNRF

Ng-F62	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
FA1090	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
1000	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
528	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGE31	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
22491	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
44-76	241	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NG6-88	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGP165	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGF26	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
2996	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
205900	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
F6124	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
90-18311	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
93-4286	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
A22	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ198	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
297-0	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ147	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ169	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ133	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGH38	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGH15	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGH36	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ232	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
BZ83	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
MC58	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
E26	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
860800	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
E32	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NGE28	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
NG3-88	212	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
SWZ107	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRVKKNDPSRFLN*
Ng-SN4	183	IHAPRTGKNIEITSLSHKYWSGKYAFARRIKKNDPSRFLN*

FIG. 13B(CONTD.)

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FIG. 14A

```
NGP165      1 MKPLILGLAAALVLSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGMLASTAEPLSEAGYYVFPAAVVEET
N_lactam    1 MKPLILGLAAVLALSACQVQKAPDFDYTAFKESKPASILVVPPLNESPDVNGTWGMLASTAEPLSEAGYYVFPAAVVEET
Ng-F62      1 MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLASTAAPFSEAGYYVFPAAVVEET
Ng-SN4      1 MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLASTAAPFSEAGYYVFPAAVVEET
FA1090      1 MKPLILGLAAVLALSACQVRKAPDLDYTSFKESKPASILVVPPLNESPDVNGTWGMLASTAAPFSEAGYYVFPAAVVEET
NG6-88      1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
1000        1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
528         1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGF26       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ198       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NG3-88      1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
297-0       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ147       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ169       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ133       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGE31       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGE28       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
SWZ107      1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGH15       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGH36       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ83        1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
44-76       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
MC58        1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
2996        1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
205900      1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
F6124       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
Z2491       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
90-18311    1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
93-4286     1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
E26         1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
860800      1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
E32         1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
NGH38       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
BZ232       1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGVLASTAAPLSEAGYYVFPAAVVEET
A22         1 MKPLILGLAAVLALSACQVQKAPDFDYTSFKESKPASILVVPPLNESPDVNGTWGMLASTAAPLSEAGYYVFPAAVVEET
```

FIG. 14A(CONTD.)

NGP165	81	FKQNGLTNAADIHAVQPEKLHQIFGNDAVLYIT[illegible]TEYGTSYQILDSVTTVSARARLVDSRNGKVLWSGSASIREGSNNSN
N_lactam	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYIT[illegible]TEYGTSYQILDSVTTVSARARLVDSRNGKVLWSGSASIREGSNNSN
Ng-F62	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
Ng-SN4	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
FA1090	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NG6-88	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
1000	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
528	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGF26	81	FKENGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ198	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NG3-88	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
297-0	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ147	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ169	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ133	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGE31	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGE28	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
SWZ107	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGH15	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGH36	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ83	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
44-76	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
MC58	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
2996	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
205900	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
F6124	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
Z2491	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
90-18311	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
93-4286	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
E26	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
860800	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
E32	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
NGH38	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
BZ232	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN
A22	81	FKQNGLTNAADIHAVRPEKLHQIFGNDAVLYITVTEYGTSYQILDSVTTVSAKARLVDSRNGKELWSGSASIREGSNNSN

FIG. 14B

```
NGP165      161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
N_lactam    161 SGLLGALVGAVVNQIANSLTDRGYQVSKAAAYDLLSPYSHNGILKGPRFVEEQPK*
Ng-F62      161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
Ng-SN4      161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
FA1090      161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSRNGILKGPRFVEEQPK*
NG6-88      161 SGLLGALVSAVVNQIANNLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
1000        161 SGLLGALVSAVVNQIANNLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
528         161 SGLLGALVSAVVNQIANNLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGF26       161 SGLLGALVSAVVNQIANNLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ198       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NG3-88      161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
297-0       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ147       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ169       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ133       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGE31       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGE28       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
SWZ107      161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGH15       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGH36       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ83        161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
44-76       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
MC58        161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
2996        161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
205900      161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
F6124       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
Z2491       161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
90-18311    161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
93-4286     161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
E26         161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
860800      161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
E32         161 SGLLGALVSAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
NGH38       161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
BZ232       161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
A22         161 SGLLGALVGAVVNQIANSLTDRGYQVSKTAAYNLLSPYSHNGILKGPRFVEEQPK*
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FIG. 15A

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2996       1 MFERSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVAE...........KETE
93-4286    1 MFERSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVAE...........KETE
BZ133      1 MFERSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVAE...........KETE
SWZ107     1 MFERSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVAE...........KETE
A22        1 MFERSVIAMACIFALSACGGGGGGICPMLNRRDTLSKPAAPVVAE...........KETE
E26        1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVAE...........KETE
1000       1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETD
528        1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
E32        1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
NG6-88     1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
NGE31      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
NGF26      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
860800     1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
NGH15      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
C11        1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
BZ198      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
NGH38      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
BZ169      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
BZ83       1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
H44-76     1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
MC58       1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
NG3-88     1 MFERSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
NGH36      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
BZ147      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
NGE28      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTPSKPAAPVVAE...........KETE
FA1090     1 MFKRSVIAMACIFPLSACGGGGGG.SPDVKSADTPSKPAAPVVAENAGEGVLPKEKKDEE
NG-F62     1 MFKRSVIAMACIFPLSACGGGGGG.SPDVKSADTPSKPAAPVVAENAGEGVLPKEKKDEE
205900     1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
90-18311   1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
NGP165     1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
Z2491      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
F6124      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
297-0      1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAAPVVSE...........KETE
BZ232      1 MFKRSVIAMACIVALSACGGGGGG.SPDVKSADTLSKPAAPVVTEDVGEEVLPKEKKDEE
N_lactam   1 MFKRSVIAMACIFALSACGGGGGG.SPDVKSADTLSKPAVPVVAEDAGEEVLPKEKKDEE
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FIG. 15A (CONTD.)

2996	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
93-4286	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
BZ133	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
SWZ107	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMLQ....
A22	50	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
E26	49	AKEDAPQAGSQGQGAPSAQGGQDMAAVSAENTGNGGAETADNPENKDEGTQNDMPQ....
1000	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
528	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
E32	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
NG6-88	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
NGE31	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
NGF26	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
860800	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGPQNDMPQ....
NGH15	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDNPKNEDEGAQNDMPQ....
C11	49	AKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGAATTDKPKNEDEGAQNDMPQ....
BZ198	49	AKEDAPQAGSQGQGAPSAQGGQDMAAVSEENTGNGGAAATDKPKNEDEGAQNDMPQNAAD
NGH38	49	AKEDAPQAGSQGQGAPSAQGGQDMAAVSEENTGNGGAAATDKPKNEDEGAQNDMPQNAAD
BZ169	49	AKEDAPQAGSQGQGAPSAQGSQDMAAVSEENTGNGGAVTADNPKNEDEVAQNDMPQNAAG
BZ83	49	AKEDAPQAGSQGQGAPSAQGSQDMAAVSEENTGNGGAVTADNPKNEDEVAQNDMPQNAAG
H44-76	49	AKEDAPQAGSQGQGAPSAQGSQDMAAVSEENTGNGGAVTADNPKNEDEVAQNDMPQNAAG
MC58	49	AKEDAPQAGSQGQGAPSAQGSQDMAAVSEENTGNGGAVTADNPKNEDEVAQNDMPQNAAG
NG3-88	49	AKEDAPQAGSQGQGAPSAQGSQDMAAVSEENTGNGGAATADNPKNEDEGAQDDMPQNAAD
NGH36	49	AKEDAPQAGSQGQGAPSAQGGQDMAAVSEENTGNGGAAATDKPKNEDEGAQNDMPQNAAD
BZ147	49	AKEDAPQAGSQGQGAPSAQGSQNMAAVSEENTGNGGAATADNPKNEDEGAQDDMPQKAAD
NGE28	49	VKEDAPQAGSQGQGAPSTQGSQDMAAVSAENTGNGGSATTDKPKNEDEGPQNDMPQNAAD
FA1090	60	AAGGAPQADT..QDATAGEGSQDMAAVSAENTGNGGAATTDNPKNEDAGAQNDMPQNAA.
NG-F62	60	AAGGAPQADT..QDATAGEGSQDMAAVSAENTGNGGAATTDNPKNEDAGAQNDMPQNAA.
205900	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
90-18311	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
NGP165	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
Z2491	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
F6124	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
297-0	49	AKEDAPQAGSQGQGAPSAQGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
BZ232	60	AVSGAPQADT..QDATAGKGGQDMAAVSAENTGNGGAATTDNPENKDEGPQNDMPQNAAD
N_lactam	60	AVGGAPQADT[illegible]QDATAGEGSQDMAAVSAENTGNGGA[illegible]TTDKPKNEDAGAQNDMPQNAAD

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FIG. 15B

```
2996       105 .......................................................N....
93-4286    105 .......................................................N....
BZ133      105 .......................................................N....
SWZ107     105 .......................................................N....
A22        106 .......................................................N....
E26        105 .......................................................N....
1000       105 .......................................................N....
528        105 .......................................................NAGNT
E32        105 .......................................................NAGNT
NG6-88     105 .......................................................NAGNT
NGE31      105 .......................................................NAGNT
NGF26      105 .......................................................NAGNT
860800     105 .......................................................NAGNT
NGH15      105 .......................................................NAGNT
C11        105 .......................................................N....
BZ198      109 .......................................................N....
NGH38      109 TDSLTPNHTPASNMPAGNMENQAPDAGESEQPANQPDMANTADGMQGDDPSAGGENAGNT
BZ169      109 TDSLTPNHTPASNMPAGNMENQAPDAGESEQPANQPDMANTADGMQGDDPSAGGENAGNT
BZ83       109 TDSSTPNHTPDPNMLAGNMENQATDAGESSQPANQPDMANAADGMQGDDPSAGGQNAGNT
H44-76     109 TDSSTPNHTPDPNMLAGNMENQATDAGESSQPANQPDMANAADGMQGDDPSAGGQNAGNT
MC58       109 TDSSTPNHTPDPNMLAGNMENQATDAGESSQPANQPDMANAADGMQGDDPSAGGQNAGNT
NG3-88     109 TDSSTPNHTPDPNMLAGNMENQATDAGESSQPANQPDMANAADGMQGDDPSAGGQNAGNT
NGH36      109 TDSLTPNHTPASNMPAVNMENQAPDTGESVQPANQPDMANAADGMQGDDPSAGGQNAGNT
BZ147      109 TDSLTPNHTPASNMPAGNMENQAPDAGESEQPANQPDMANTADGMQGDDPSAGGENAGNT
NGE28      109 TDSLTPNHTPAPNMPAGNMENQATDAGESEQPANQPDMANTADGMQGDDPSAGGENAGNT
FA1090     117 TDSLTPNHTPAPNMPTGDMGNQAPDYGESAQPENQPDAANAGDGIQGDDPSAGGENAGNT
NG-F62     117 ............................................................
205900     118 ............................................................
90-18311   118 TDSSTPNHTPAPNMPTRDMGNQAPDAGESAQPANQPDMANAADGMQGDDPSA.GENAGNT
NGP165     118 TDSSTPNHTPAPNMPTRDMGNQAPDAGESAQPANQPDMANAADGMQGDDPSA.GENAGNT
Z2491      118 TDSSTPNHTPAPNMPTRDMGNQAPDAGESAQPANQPDMANAADGMQGDDPSA.GENAGNT
F6124      118 TDSSTPNHTPAPNMPTRDMGNQAPDAGESAQPANQPDMANAADGMQGDDPSA.GENAGNT
297-0      109 TDSSTPNHTPAPNMPTRDMGNQAPDAGESAQPANQPDMANAADGMQGDDPSA.GENAGNT
BZ232      118 TDSSTPNHTPAPNMPTRDMGNQAPDSGESAQPANQPDMANAADGIQGDDPSV.GENAGNT
N_lactam   118 TDSLTPNYTTAPNMPAVDMGNQAPDSGESAQPANQPDMANAADGIQGDDPSV.GENAGNT
```

FIG. 15B(CONTD.)

2996	106	SAESANQTGNNQPADSSDSAPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
93-4286	106	SAESANQTGNNQPADSSDSAPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
BZ133	106	SAESANQTGNNQPADSSDSAPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
SWZ107	106	SAESANQTGNNQPADSSDSAPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
A22	107	SAESANQTGNNQPADSSDSAPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
E26	106	AAESANQTGNNQSAGSSDSAPASNPAPANGGGDFGRTNVGNSVVIDGPSQNITLTHCKGD
1000	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
528	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
E32	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
NG6-88	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
NGE31	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
NGF26	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
860800	110	AAQGTNQAENNQVGGSQNPAPSSNPNATN.GGNFGRVDLANGVLIDGPSQNITLTHCKSD
NGH15	106	AAESANQTGNNQPAGSQNPAPSTNPNATNGGGNFGRVDLANGVLIDGPSQNITLTHCKGD
C11	106	AAESANQAEKNQVGGSQNPASSTNPNATN.GGNFGRVDLANGIKLDSGSENVTLTHCKDK
BZ198	169	AAQGTNQAENNQTAGSQNPASSTNPSATNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGD
NGH38	169	AAQGTNQAENNQTAGSQNPASSTNPSATNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGD
BZ169	169	AAQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
BZ83	169	AAQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
H44-76	169	AAQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
MC58	169	AAQGANQAGNNQAAGSSDPIPASNPAPANGGSNFGRVDLANGVLIDGPSQNITLTHCKGD
NG3-88	169	AAQGANQAGNNQAAGSSDPIPASNPATTNSGGDFGRTNVANGIKLDGPSQNITLTHCK.D
NGH36	169	AAQGANQAGNNQAAGSSDPIPASNPATTNSGGDFGRTNVANGIKLDGPSQNITLTHCK.D
BZ147	169	AAQGANQAGNNQAAGSSDSTPASNSATTNSGSDFGRTNVANGVLIDGPSQNITLTHCKGD
NGE28	169	AAQGTNQAENNQAAGSQNPASSTNPSTTNSGGDFGRTNVGNSVVIDGPSQNITLTHCKGD
FA1090	117	..ESANQTGNNQPAGSSDSAPASNPAPANGGSDFGRTNVGNSVVIDGPSQNITLTHCKGD
NG-F62	117	..ESANQTGNNQPAGSSDSAPASNPAPANGGSDFGRTNVGNSVVIDGPSQNITLTHCKGD
205900	177	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
90-18311	177	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
NGP165	177	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
Z2491	177	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
F6124	177	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
297-0	168	ADQAANQAENNQVGGSQNPASSTNPNATNGGSDFGRINVANGIKLDSGSENVTLTHCKDK
BZ232	177	ADQAENQAENNQAAGSQNPASSTNPNATNGGGDFGRTNVGNSVVIDGPSQNITLTHCKGD
N_lactam	177	ADQAENQAENNQ[illegible]AGSQNPASSTNPNATNGGGDFGRTN[illegible]GNSVVIDGPSQNITLTHCKGD

FIG. 15C

```
2996       166 SCNGDNLLDEEAPSKSEFENLNESERIEKYKK....DGKSDKFTNLVATAVQANGTNKYV
93-4286    166 SCNGDNLLDEEAPSKSEFENLNESERIEKYKK....DGKSDKFTNLVATAVQANGTNKYV
BZ133      166 SCNGDNLLDEEAPSKSEFENLNESERIEKYKK....DGKSDKFTNLVATAVQANGTNKYV
SWZ107     166 SCNGDNLLDEEAPSKSEFENLNESERIEKYKK....DGKSDKFTNLVATAVQANGTNKYV
A22        167 SCNGDNLLDEEAPSKSEFENLNESERIEKYKK....DGKSDKFTNLVATAVQANGTNKYV
E26        166 SCDGDNLLDEEAPSKSEFDNLSESERMEKYKK....DGKSDKFTGFVADKLQMKGTNQYI
1000       169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
528        169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
E32        169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
NG6-88     169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
NGE31      169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
NGF26      169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
860800     169 SCNGDNLLSEEAPSKSEFEQLSDEDKIKKYKK....DG..EKFTGLVADRLQMKGTNQYI
NGH15      166 SCNGDNLLAEEAPSKSEFEKLSDEDKISNYKK....DGK.DKFVGLIADRVKKDGTNKYI
C11        165 VCDRD.FLDEEAPSKSEFESLDDSGRINKYKK....DGKSDKFTNLVATEVQANGVNKYV
BZ198      229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKKDGKNDGKNDKFVGLVADSVQMKGINQYI
NGH38      229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKKDGKNDGKNDKFVGLVADSVQMKGINQYI
BZ169      229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYI
BZ83       229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYI
H44-76     229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYI
MC58       229 SCSGNNFLDEEVQLKSEFEKLSDADKISNYKK....DGKNDKFVGLVADSVQMKGINQYI
NG3-88     228 TVCGSNFLAEEAPSKSEFESLDDSGRINKYKK....DGQ.DKFTNLVATEVKANGTNKYV
NGH36      228 TVCGSNFLAEEAPSKSEFESLDDSGRINKYKK....DGQ.DKFTNLVATEVKANGTNKYV
BZ147      229 SCSGDNLLDEEAPPKSEFENLSDEEKIKRYKK....DGK.N.FTGLVATKVEKKGVNKYV
NGE28      229 SCNDDNLLYEEAPSKSEFESLSDEKKIEKYKK....DG..EKFTGLVAIKVENNGLNKYT
FA1090     175 SCNGDNLLDEEAPSKSEFEKLSDEEKIKRYKK....DEQRENFVGLVADRVKKDGTNKYI
NG-F62     175 SCNGDNLLDEEAPSKSEFEKLSDEEKIKRYKK....DEQRENFVGLVADRVKKDGTNKYI
205900     237 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
90-18311   237 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
NGP165     237 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
Z2491      237 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
F6124      237 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
297-0      228 VCDRD.FLDEEAPPKSEFEKLSDEEKINKYKK....DEQRENFVGLVADRVEKNGTNKYV
BZ232      237 SCDGDNLLDEEAPSKSEFDNLSESERMEKYKK....DGKSDKFTGFVADKLQMKGTNQYI
N_lactam   237 SCNDDNLLYEEAPSKSEFESLNDSGRIDKYKK....DGQ.DKFTNLVATKVEKKGLNKYV
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FIG. 15C(CONTD.)

```
2996       222 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
93-4286    222 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
BZ133      222 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
SWZ107     222 IIYKDKSASSSFARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
A22        223 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
E26        222 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
1000       223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
528        223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
E32        223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NG6-88     223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGE31      223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGF26      223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
860800     223 IFYKPKTTSS..ARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGH15      221 IFYTDKPPT.......RSARSRRSLPAEIPLIPVNQADTLIVDGEAVSLTGYSGNIFAPE
C11        220 IIYKDKSASS..AQFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
BZ198      289 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGH38      289 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
BZ169      285 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
BZ83       285 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
H44-76     285 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
MC58       285 IFYKPKPTS..FARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NG3-88     283 IIYKDKSTS..SARVRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGH36      283 IIYKDKSTS..SARVRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVILTGHSGNIFEPE
BZ147      283 IIYTDKTPT.......RSARSRRSLSEEMPLIPVNQADTLIVDGEAVSLTGHSGNIFALE
NGE28      283 IIYQAQPT........RSARSRRSLPAEMPLIPVNQVDTLIVDGEAVSLTGHSGNIFAPE
FA1090     231 IFYTDKPPT.......RSARSRRSLPAEIPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NG-F62     231 IFYTDKPPT.......RSARSRRSLPAEIPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
205900     292 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
90-18311   292 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
NGP165     292 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
Z2491      292 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
F6124      292 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
297-0      283 IIYKDKSASSSSARFRRSARSRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
BZ232      293 IFYKPK..TTSSARFRRSARLRRSLPAEMPLIPVNQADTLIVDGEAVSLTGHSGNIFAPE
N_lactam   292 IFY..T..DTPP[illegible]SARSRRLRRSLPAEMPLIPVNQAD[illegible]IVDGEAVSLTGHSGNIFAPE
```

FIG. 15D

2996	282	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
93-4286	282	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
BZ133	282	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
SWZ107	282	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
A22	283	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
E26	280	GNYRYLTYGAEKLSGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPSRGRFA
1000	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
528	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
E32	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
NG6-88	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
NGE31	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
NGF26	281	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTKGRFA
860800	281	GNYRYLTYGAEKLSGGSYALSVQGKPAKGEMLAGTAVYNGEVLHFHTENGRSYPTRGRFA
NGH15	274	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGAAVYNGEVLHFHMENGRPYPSGGRFA
C11	278	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYSGEVLHFHTENGRPYPSRGRFA
BZ198	347	GNYRYLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHTENGRPSPSRGRFA
NGH38	347	GNYRYLTYGAEKLPGGSYALRVQGEPSKGEMLAGTAVYNGEVLHFHTENGRPSPSRGRFA
BZ169	343	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFA
BZ83	343	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFA
H44-76	343	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFA
MC58	343	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRPYPTRGRFA
NG3-88	341	GNYRYLTYGAEKLSGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPTRGRFA
NGH36	341	GNYRYLTYGAEKLSGGSYALRVKGEPAKGEMLAGTAVYNGEVLHFHTENGRSYPTRGRFA
BZ147	336	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLAGAAVYNGEVLHFHTENGRSYPTRGRFA
NGE28	335	GNYRYLTYGAEKLSGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPFRGRFA
FA1090	284	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLVGTAVYNGEVLHFHMENGRPYPSGGRFA
NG-F62	284	GNYRYLTYGAEKLPGGSYALRVQGEPAKGEMLVGTAVYNGEVLHFHMENGRPYPSGGRFA
205900	352	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFA
90-18311	352	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFA
NGP165	352	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFA
Z2491	352	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFA
F6124	352	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSLSGGRFA
297-0	343	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHMENGRPSPSGGRFA
BZ232	351	GNYRYLTYGAEKLSGGSYALSVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPSRGRFA
N_lactam	348	GNYRYLTYRAEKLSGGSYALRVQGEPAKGEMLAGTAVYNGEVLHFHTENGRPYPSGGRFA

FIG. 15D(CONTD.)

2996	342	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
93-4286	342	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
BZ133	342	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
SWZ107	342	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
A22	343	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
E26	340	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
1000	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
528	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
E32	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NG6-88	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NGE31	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NGF26	341	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
860800	341	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGNWTENGGGDVSGRFYGPAGEEV
NGH15	334	AKVNFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
C11	338	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
BZ198	407	AKVDFGSKSVDGIIDSGDGLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEV
NGH38	407	AKVDFGSKSVDGIIDSGDGLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEV
BZ169	403	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
BZ83	403	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
H44-76	403	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
MC58	403	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
NG3-88	401	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGRFYGPGGEEV
NGH36	401	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGKFYGPAGEEV
BZ147	396	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NGE28	395	AKVDFGSKSVDGIIDSGDDLHMGKQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
FA1090	344	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NG-F62	344	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
205900	412	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
90-18311	412	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
NGP165	412	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
Z2491	412	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
F6124	412	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
297-0	403	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAVIDGNGFKGTWTENGGGDVSGRFYGPAGEEV
BZ232	411	AKVDFGSKSVDGIIDSGDDLHMGTQKFKAAIDGNGFKGTWTENGSGDVSGKFYGPAGEEV
N_lactam	408	AKVDFGSKSVDGI[illegible]SGDDLHMGTQKFKAAIDGNGFKGT[illegible]ENGGGDVSGRFYGPAGEEV

FIG. 15E

2996	402	AGKYSYRPTDAEKGGFGVFAGKKEQD
93-4286	402	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ133	402	AGKYSYRPTDAEKGGFGVFAGKKEQD
SWZ107	402	AGKYSYRPTDAEKGGFGVFAGKKEQD
A22	403	AGKYSYRPTDAEKGGFGVFAGKKEQD
E26	400	AGKYSYRPTDAEKGGFGVFAGKKEQD
1000	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
528	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
E32	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
NG6-88	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGE31	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGF26	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
860800	401	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGH15	394	AGKYSYRPTDAEKGGFGVFAGKKEQD
C11	398	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ198	467	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGH38	467	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ169	463	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ83	463	AGKYSYRPTDAEKGGFGVFAGKKEQD
H44-76	463	AGKYSYRPTDAEKGGFGVFAGKKEQD
MC58	463	AGKYSYRPTDAEKGGFGVFAGKKEQD
NG3-88	461	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGH36	461	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ147	456	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGE28	455	AGKYSYRPTDAEKGGFGVFAGKKEQD
FA1090	404	AGKYSYRPTDAEKGGFGVFAGKKDRD
NG-F62	404	AGKYSYRPTDAEKGGFGVFAGKKDRD
205900	472	AGKYSYRPTDAEKGGFGVFAGKKEQD
90-18311	472	AGKYSYRPTDAEKGGFGVFAGKKEQD
NGP165	472	AGKYSYRPTDAEKGGFGVFAGKKEQD
Z2491	472	AGKYSYRPTDAEKGGFGVFAGKKEQD
F6124	472	AGKYSYRPTDAEKGGFGVFAGKKEQD
297-0	463	AGKYSYRPTDAEKGGFGVFAGKKEQD
BZ232	471	AGKYSYRPTDAEKGGFGVFAGKKEQD
N_lactam	468	AGKYSYRPTDAEKGGFGVFAGKKEQD

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FIG. 16A

NGE28	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
F6124	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
E32	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGE31	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
2996	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
860800	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NG6-88	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
BZ169	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGF26	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGH38	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
SWZ107	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
BZ232	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
BZ83	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
44-76	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
MC58	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
E26	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
BZ198	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NG3-88	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
297-0	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
1000	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
BZ147	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
528	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGP165	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGH15	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
NGH36	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
90-18311	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
93-4286	1	MEFFIILLVAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
Ng-F62	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
Ng-SN4	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
FA1090	1	MEFFIILLAAVAVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
205900	1	MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
Z2491	1	MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL
A22	1	MEFFIILLAAVVVFGFKSFVVIPQQEVHVVERLGRFHRALTAGLNILIPFIDRVAYRHSLKEIPLDVPSQVCITRDNTQL

FIG. 16A(CONTD.)

NGE28	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSIVVSALDEAAGAWGVKVLRYEIKD
F6124	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSIVVSALDEAAGAWGVKVLRYEIKD
E32	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSIVVSALDEAAGAWGVKVLRYEIKD
NGE31	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
2996	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
860800	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
NG6-88	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
BZ169	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
NGF26	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
NGH38	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
SWZ107	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
BZ232	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
BZ83	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
44-76	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
MC58	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
E26	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
BZ198	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD
NG3-88	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
297-0	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
1000	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
BZ147	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
528	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
NGP165	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
NGH15	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
NGH36	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
90-18311	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
93-4286	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
Ng-F62	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
Ng-SN4	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
FA1090	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
205900	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
Z2491	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVSALDEAAGAWGVKVLRYEIKD
A22	81	TVDGIIYFQVTDPKLASYGSSNYIMAITQLAQTTLRSVIGRMELDKTFEERDEINSTVVAALDEAAGAWGVKVLRYEIKD

FIG. 16B

NGE28	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
F6124	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
E32	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGE31	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
2996	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
860800	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NG6-88	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
BZ169	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGF26	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGH38	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
SWZ107	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
BZ232	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
BZ83	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
44-76	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
MC58	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
E26	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
BZ198	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NG3-88	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
297-0	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
1000	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
BZ147	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
528	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGP165	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGH15	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
NGH36	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
90-18311	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
93-4286	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
Ng-F62	161	LVPPQEILRAMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
Ng-SN4	161	LVPPQEILRAMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
FA1090	161	LVPPQEILRAMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
205900	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
Z2491	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR
A22	161	LVPPQEILRSMQAQITAEREKRARIAESEGRKIEQINLASGQREAEIQQSEGEAQAAVNASNAEKIARINRAKGEAESLR

FIG. 16B(CONTD.)

NGE28	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
F6124	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
E32	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGE31	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
2996	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
860800	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NG6-88	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
BZ169	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGF26	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGH38	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
SWZ107	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
BZ232	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
BZ83	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
44-76	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
MC58	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
E26	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
BZ198	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NG3-88	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
297-0	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
1000	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
BZ147	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
528	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGP165	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGH15	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
NGH36	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
90-18311	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
93-4286	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
Ng-F62	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
Ng-SN4	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
FA1090	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
205900	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
Z2491	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*
A22	241	LVAEANAEAIRQIAAALQTQGGADAVNLKIAEQYVAAFNNLAKESNTLIMPANVADIGSLISAGMKIIDSSKTAK*

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FIG. 17

```
1000     1  MTIYFKNGFYDDTLGGIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSEY
F6124    1  MTIYFKNGFYDDTLGGIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSEY
C11      1  MTIYFKNGFYDDTLGSIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSEY
2996     1  ~~~~~~NGFYDDTLGSIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSDY
BZ133    1  MTIYFKNGFYDDTLGSIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSDY
MC58     1  MTIYFKNGFYDDTLGGIPEGAVAVRAEEYAALLAGQAQGGQIAADSDGRPVLTPPRPSDY
NGH38    1  ~~~ISKTGFYDDTLGSIPEGAVAVRAEEYAALLAGQTQGGQIAADSDGRPVLTPPRPSEY
BZ232    1  ~~IYFKNGFYDDTLGSIPEGAVAVRAEEYAALLAGQTQGGQIAADSDGRPVLTPPRPSEY

1000    61  HEWDGKKWEIGEAAAAARFAEQKTATAFRLAAKADELKNSLLAGYPQVEIDSFYRQEKEA
F6124   61  HEWDGKKWEIGEAAAAARFAEQKTATAFRLAAKADELKNSLLAGYPQVEIDSFYRQEKEA
C11     61  HEWDGKKWEIGEAAAAARFAEQKTATAFRLAAKADELKNSLLAGYPQVEIDSFYRQEKEA
2996    55  HEWDGKKWKISKAAAAARFAEQKTATAFRLAEKADELKNSLLAGYPQVEIDSFYRQEKEA
BZ133   61  HEWDGKKWKIGKAAAAARFAEQKTATAFRLAEKADELKNSLLAGYPQVEIDSFYRQEKEA
MC58    61  HEWDGKKWKISKAAAAARFAKQKTALAFRLAEKADELKNSLLAGYPQVEIDSFYRQEKEA
NGH38   58  HEWDGKKWEIGEAAAAARFAEQKTATAFRLAAKADELKNSLLAGYPQVEIDSFYRQEKEA
BZ232   59  HEWDGKKWEIGEAAAAARFAEQKTATAFRLAAKADELKNSLLAGYPQVEIDSFYRQEKEA
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FIG. 17 (CONTD.)

```
1000     121  LARQADNNAPTPMLAQIAATRGVELDVLIEKVIEKSARLAVAAGAIIGK....RQQLEDK
F6124    121  LARQADNNAPTPMLAQIAATRGVELDVLIEKVIEKSARLAVAAGAIIGK....RQQLEDK
C11      121  LARQADNNAPTPMLAQIAAARGVELDVLIEKVVEKSARLAVAAGAIIGK....RQQLEDK
2996     115  LARQADNNAPTPMLAQIAAARGVELDVLIEKVVEKSARLAVAAGAIIGK....RQQLEDK
BZ133    121  LARQADNNAPTPMLAQIAAARGVELDVLIEKVVEKSARLAVAAGAIIGK....RQQLEDK
MC58     121  LARQADNNAPTPMLAQIAAARGVELDVLIEKVIEKSARLAVAAGAIIGK....RQQLEDK
NGH38    118  LARQADNNAPTPMLAQIAAARGVELDVLIEKVVEKSARLAVAAGAIIGK....RQQLEDK
BZ232    119  LARQADNNAPTPMLAQIAAARGVELDVLIEKVVEKSARLAVAAGAIIGKPAAARRQIEHH

1000     177  LNTIETAPGLDALEKEIEEWTLNIG
F6124    177  LNTIETAPGLDALEKEIEEWTLNIG
C11      177  LNTIETAPGLDALEKEIEEWTLNIG
2996     171  LNAIETAPGLDALEKEIE~~~~~~~
BZ133    177  LNAIETAPGLDALEKEIEEWTLNIG
MC58     177  LNTIETAPGLDALEKEIEEWTLNIG
NGH38    174  LNAIETAPGLDALEKEIE~~~~~~~
BZ232    179  RN...PRPGLDALEKEIEEWTA~~~
```

FIG. 18A

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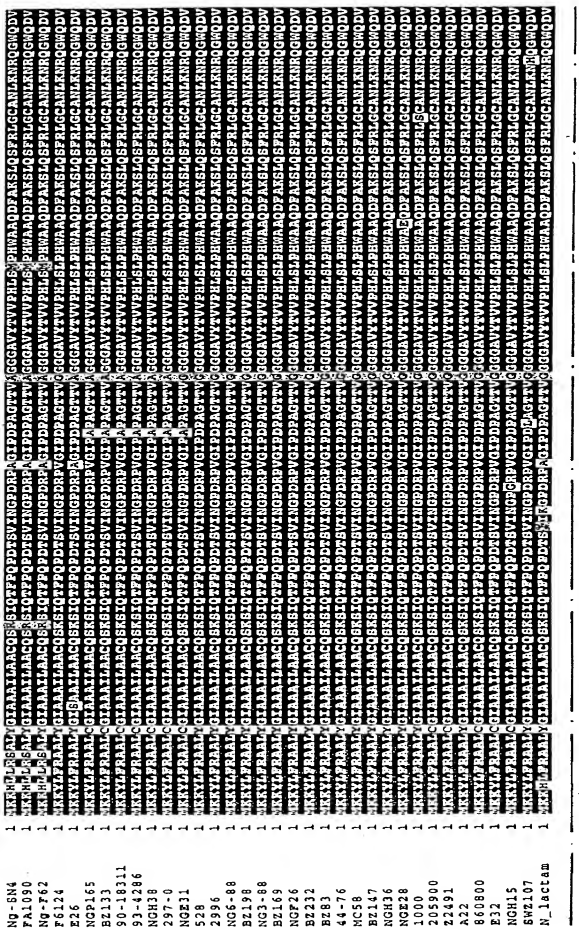

FIG. 18A(CONTD.)

Ng-SN4	101	CAQAFQTPIHSFQAKRFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKNLVRIRQTGKNSGTIDNAGGT
FA1090	101	CAQAFQTPVHSFQAKRFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKNLVRIRQTGKNSGTIDNAGGT
Ng-F62	101	CAQAFQTPVHSFQAKRFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDGRRTERARFPIYGIPDDFISVPLPAGLRGGKALVRIRQTGKNSGTIDNAGGT
F6124	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT
E26	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT
NGP165	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ133	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
90-18311	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
93-4286	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NGH38	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT
297-0	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT
NGE31	101	CAQAFQTPVHSVQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT
528	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
2996	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NG6-88	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ198	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NG3-88	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ169	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NGF26	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ232	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ83	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
44-76	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
MC58	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
BZ147	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NGH36	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NGE28	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
1000	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
205900	101	CAQAFQTPVHSVQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
Z2491	101	CAQAFQTPVHSVQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
A22	101	CAQAFQTPVHSVQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
860800	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
E32	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
NGH15	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
SWZ107	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNTGGT
N_lactam	101	CAQAFQTPVHSFQAKQFFERYFTPWQVAGNGSLAGTVTGYYEPVLKGDDRRTAQARFPIYGIPDDFISVPLPAGLRSGKALVRIRQTGKNSGTIDNAGGT

FIG. 18B

Ng-SN4	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
FA1090	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
Ng-F62	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
F6124	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
E26	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
NGP165	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ133	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
90-18311	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
93-4286	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
NGH38	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
297-0	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NGE31	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
528	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
2996	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NG6-88	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ198	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NG3-88	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ169	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NGF26	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ232	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ83	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
44-76	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
MC58	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
BZ147	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NGH36	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
NGE28	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
1000	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
205900	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
Z2491	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
A22	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
860800	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
E32	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL
NGH15	201	HTADLSQFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
SWZ107	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGKYMADKGYL
N_lactam	201	HTADLSRFPITARTTAIKGRFEGSRFLPYHTRNQINGGALDGKAPILGYAEDPVELFFMHIQGSGRLKTPSGKYIRIGYADKNEHPYVSIGRYMADKGYL

FIG. 18B (CONTD.)

Ng-SN4	301	KLGQTSMQGIRSYMRQNPHKLAEVLGQNPSYIFFRELAGSGNEGPVGALGTPLMGEYAGAIDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
FA1090	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSGNEGPVGALGTPLMGEYAGAIDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
Ng-F62	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSGGDGPVGALGTPLMGGYAGAIDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
F6124	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTSKALNRLIMAQDTGSAIKG
E26	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGP165	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ133	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
90-18311	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
93-4286	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGH38	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSRNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
297-0	301	KLGQTSMQGIRAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGE31	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
528	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
2996	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NG6-88	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ198	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NG3-88	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ169	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGF26	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ232	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ83	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
44-76	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
MC58	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
BZ147	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGH36	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
NGE28	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
1000	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
205900	301	KLGQTSMQGIRAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
Z2491	301	KLGQTSMQGIRAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
A22	301	KLGQTSMQGIRAYMQQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
860800	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYIFFRELAGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
E32	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATTHPITRKALNRLIMAQDTGSAIKG
NGH15	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSSNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
SWZ107	301	KLGQTSMQGIRSYMRQNPQRLAEVLGQNPSYIFFRELTGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG
N_lactam	301	KLGQTSMQGIRAYMRQNPQRLAEVLGQNPSYVFFRELAGSGNDGPVGALGTPLMGEYAGAVDRHYITLGAPLFVATAHPVTRKALNRLIMAQDTGSAIKG

FIG. 18C

Ng-SN4	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
FA1090	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
Ng-F62	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
F6124	401	AVRVDYFWGYGDEAGETAGKMKEPGYVWQLLPNGMKPEYRP*
E26	401	AVRVDYFWGYGDEAGETAGKMKEPGYVWQLLPNGMKPEYRP*
NGP165	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ133	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
90-18311	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
93-4286	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGH38	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
297-0	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGE31	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
528	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
2996	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NG6-88	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ198	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NG3-88	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ169	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGF26	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ232	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ83	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
44-76	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
MC58	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
BZ147	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGH36	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGE28	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
1000	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
205900	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
Z2491	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
A22	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
860800	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
E32	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
NGH15	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
SWZ107	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*
N_lactam	401	AVRVDYFWGYGDEAGELAGKQKTTGYVWQLLPNGMKPEYRP*

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FIG. 19

1000	1	MKKIIIAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
C11	1	MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
2996	1	MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
BZ133	1	MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
BZ232	1	MKKIIFAALAAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
NGH38	1	MKKIIFAALEAAAVGTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
MC58	1	MKKIIFAALAAAAISTASAATYKVDEYHANARFAIDHFNTSTNVGGFYGLTGSVEFDQAK
F6124	1	MKKIIIAALAAAAIGTASAATYKVDEYHANARFSIDHFNTSTNVGGFYGLTGSVEFDQAK

1000	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
C11	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
2996	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
BZ133	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
BZ232	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
NGH38	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
MC58	61	RDGKIDITIPIANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL
F6124	61	RDGKIDITIPVANLQSGSQHFTDHLKSADIFDAAQYPDIRFVSTKFNFNGKKLVSVDGNL

FIG. 19(CONTD.)

```
1000    121  TMHGKTAPVKLKAEKFNCYQSPMEKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
C11     121  TMHGKTAPVKLKAEKFNCYQSPMEKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
2996    121  TMHGKTAPVKLKAEKFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
BZ133   121  TMHGKTAPVKLKAEKFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
BZ232   121  TMHGKTAPVKLKAEKFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
NGH38   121  TMHGKTAPVKLKAEKFNCYQSPMAKTEVCGGDFSTTIDRTKWGVDYLVNVGMTKSVRIDI
MC58    121  TMHGKTAPVKLKAEKFNCYQSPMEKTEVCGGDFSTTIDRTKWGMDYLVNVGMTKSVRIDI
F6124   121  TMHGKTAPVKLKAEKFNCYQSPMLKTEVCGGDFSTTIDRTKWGMDYLVNVGMTKSVRIDI

1000    181  QIEAAKQ~
C11     181  QIEAAKQ~
2996    181  QIEAAKQ~
BZ133   181  QIEAAKQ~
BZ232   181  QIEAAKQ~
NGH38   181  QIEAAKQ~
MC58    181  QIEAAKQ*
F6124   181  QIEAAKQ~
```

FIG. 20A Orf 4 (33 kD)

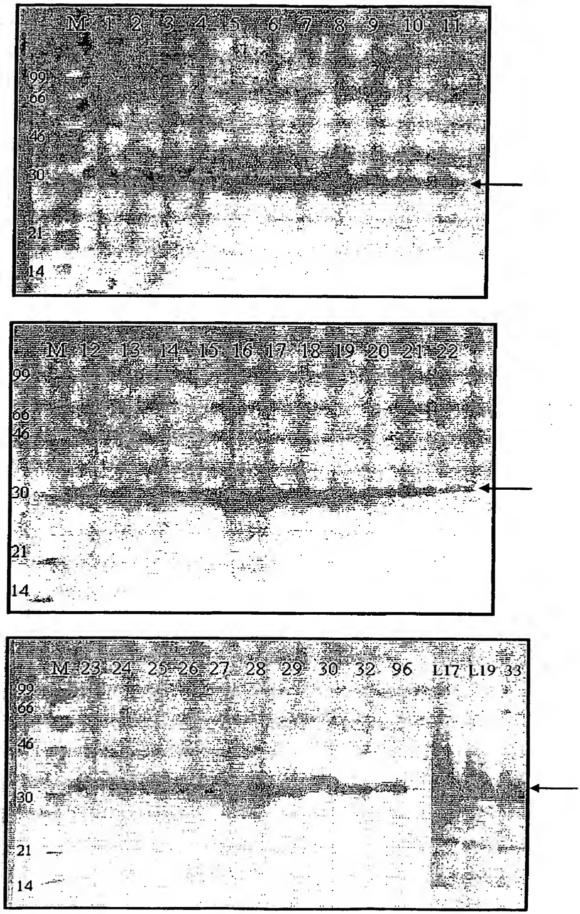


FIG. 20B 225 (27kD)*

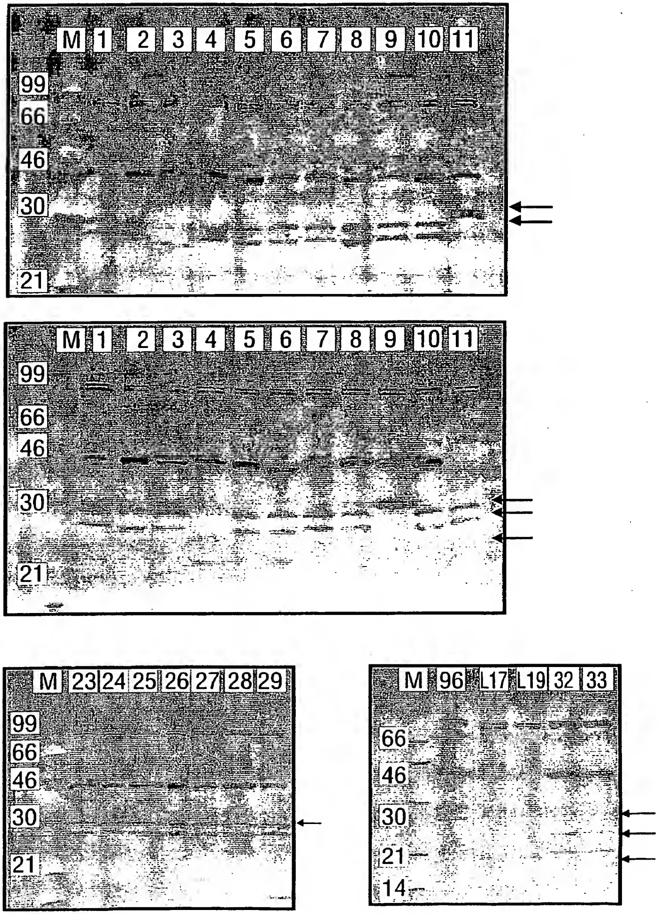


FIG. 20C 235 (23 kD)

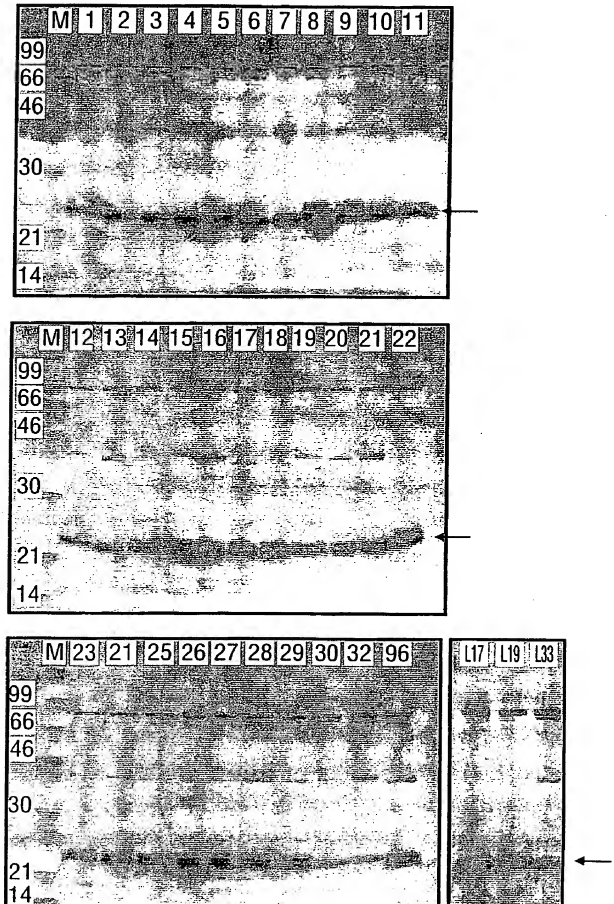


FIG. 20D 519 (35 kD)

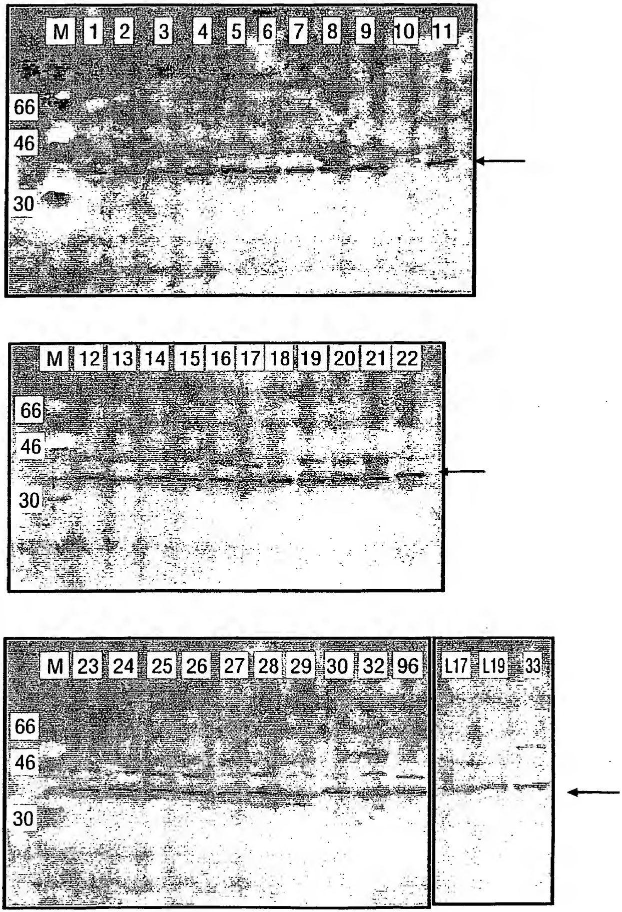
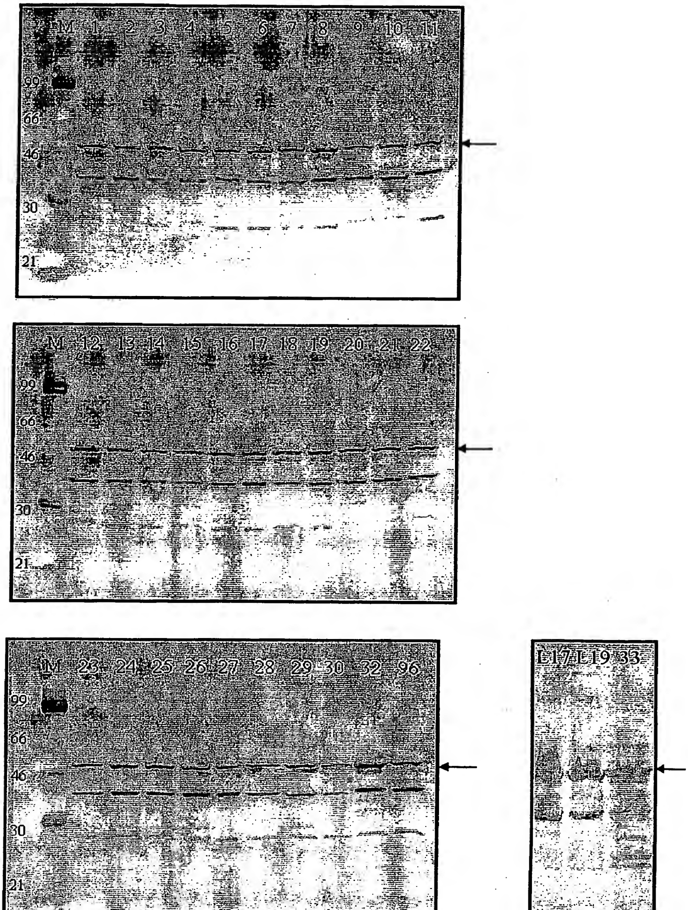


FIG. 20E 919 (48kD)



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(74) Agents: HALLYBONE, Huw, George et al.; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 13 June 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONSERVED NEISSERIAL ANTIGENS

(57) Abstract: To ensure maximum cross-strain recognition and reactivity, regions of proteins that are conserved between different Neisserial species, serogroups and strains can be used. The invention provides proteins which comprise stretches of amino acid sequence that are shared across the majority of *Neisseria*, particularly *N. meningitidis* and *N.gonorrhoeae*.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/00642

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C07K14/22 C12Q1/68 G01N33/53 A61K39/095

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N C12Q G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COONEY ET AL.: "Three contiguous lipoprotein genes in Pasteurella haemolytica A1 which are homologous to a lipoprotein gene in Haemophilus influenza Type b" INFECTION AND IMMUNITY, vol. 61, no. 11, November 1993 (1993-11), pages 4682-4688, XP002148894 abstract page 4682, column 1 figures 3,4 ---	1,3-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 2000	22. 12. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van Klompenburg, W

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International Application No
PCT/IB 00/00642

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE SWISSPROT [Online] ACC. NO.: p28635, 1 December 1992 (1992-12-01) GERVAIS ET AL.: "putative lipoprotein yaec precursor" XP002148895 abstract	1,3-11, 15
X	EP 0 273 116 A (MAX PLANCK GESELLSCHAFT) 6 July 1988 (1988-07-06) page 3, line 12 - line 25 page 3, line 42 - line 47 claims 1-23; figure 1; examples 1-4	1-7
X	WO 96 29412 A (IAF BIO VAC INC ;BRODEUR BERNARD R (CA); MARTIN DENIS (CA); HAMEL) 26 September 1996 (1996-09-26) page 5, line 24 -page 6, line 12 claims 1-90; figures 11,12,15; examples 4,7,9; table 2	1-7
X	PETTERSSON A ET AL: "Sequence variability of the meningococcal lactoferrin-binding protein LbpB" GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 231, no. 1-2, 29 April 1999 (1999-04-29), pages 105-110, XP004166783 ISSN: 0378-1119 page 105, column 2 page 109, column 2 -page 110, column 1; figures 1,2	1-7
P,X	WO 99 24578 A (PIZZA MARIAGRAZIA ;SCARLATO VINCENZO (IT); RAPPUOLI RINO (IT); CHI) 20 May 1999 (1999-05-20) cited in the application page 164, line 42 -page 169, line 34	1-15

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INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/IB 00/00642

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15 all partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15, all partially

   A protein comprising a conserved fragment of ORF4 with SEQ ID NOs: 22-53. The above mentioned protein for use as a medicament. A nucleic acid encoding the above mentioned protein. The use of the above mentioned protein or nucleic acid in the manufacture of a medicament. The use of the above mentioned protein or nucleic acid in the manufacture of a multi-specific diagnostic reagent.

2. Claims: 1-15, all partially

   Idem for ORF40 with SEQ ID NOs: 1-21

3. Claims: 1-15, all partially

   Idem for ORF46 with SEQ ID NOs: 182-187

4. Claims: 1-15, all partially

   Idem for protein 225 for SEQ ID NOs: 54-87

5. Claims: 1-15, all partially

   Idem for protein 235 with SEQ ID NOs: 88-118

6. Claims: 1-15, all partially

   Idem for protein 287 for SEQ ID NOs: 119-124

7. Claims: 1-15, all partially

   Idem for protein 519 with SEQ ID NOs: 125-146

8. Claims: 1-15, all partially

   Idem for protein 726 with SEQ ID NOs: 188-195

9. Claims: 1-15, all partially

   Idem for protein 919 with SEQ ID NOs: 147-181

10. Claims: 1-15, all partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Idem for protein 953 with SEQ ID NOs: 196-203

11. Claims: 1-15 all partially

A protein comprising a conserved fragment of a Neisserial protein not covered by the above mentioned inventions. medicament. A nucleic acid encoding the above mentioned protein. The use of the above mentioned protein or nucleic acid in the manufacture of a medicament. The use of the above mentioned protein or nucleic acid in the manufacture of a multi-specific diagnostic reagent.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 00/00642

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0273116	A	06-07-1988	NONE			
WO 9629412	A	26-09-1996	AU	716225	B	24-02-2000
			AU	4934396	A	08-10-1996
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			JP	11500624	T	19-01-1999
			NO	974264	A	13-11-1997
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			SI	9620035	A	31-12-1998
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			EP	1029052	A	23-08-2000